

THE

AMERICAN JOURNAL

OF THE

MEDICAL SCIENCES

EDITED BY

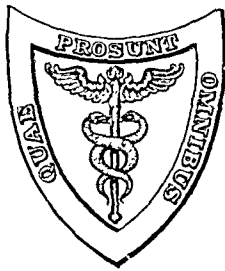
JOHN H. MUSSER, JR., M.D.

E. B. KRUMBHAAR, M.D.

ASSISTANT EDITOR

NEW SERIES

VOL. CLXVII



LEA & FEBIGER

PHILADELPHIA AND NEW YORK

1924

COPYRIGHT
LEA & FEBIGER
1924

CONTENTS OF VOL. CLXVII

ORIGINAL ARTICLES

The Significance of Glycosuria in Gall-bladder and Duct Diseases. By JOHN A. LICHTY, M.PH., M.D., and JOHN O. WOODS, A.B., M.D.	1
The Spleen and Digestion. Study IV. The Spleen and Biliary Secretion; the Reaction in Bile-pigment Secretion following Splenectomy. By WILLIAM DEP. INLOW, M.D.	10
Blood Counts and Basal Metabolism of Leukemias under Roentgen-ray Treatment. By KENNETH R. McALPIN, M.D. and BERTRAM J. SANGER, M.D.	29
Roentgen-ray Therapy in the Treatment of Exophthalmic Goiter. By G. M. GOODWIN, M.D., and W. B. LONG, M.D.	38
Sporotrichosis. By HARRY R. FOERSTER, B.S., M.D.	54
An Unusual Malignant Tumor of the Pancreas. By N. C. FOOT, M.D., B. N. CARTER, M.D., and M. J. FLIPSE, M.D.	76
Torula Infection in Man. By W. M. SHEPPE, M.D.	91
The Relation of the Non-protein Nitrogen of the Blood to Parathyroid Tetany. By RUSSELL L. HADEN, M.D., and THOMAS G. ORR, M.D.	108
The Action of Intravenous Injections of Sodium Bicarbonate upon the Kidneys. By ELLIS KELLERT, M.D.	114
Palpation of the Spleen. By WILLIAM S. MIDDLETON, M.D.	118
The Clinical Significance of the Pathological Changes in Hodgkin's Disease. By DOUGLAS SYMMERS, M.D.	157
Tuberculosis as an Etiological Factor in Hodgkin's Disease: A Historical Review. By WILLIS S. LEMON, M.B. (TOR.)	178
Management of the Diabetic Patient, with Especial Reference to the Administration of Insulin. By WILLARD C. STONER, M.D.	189

Practical Considerations in the Management of Patients Presenting Essential Hypertension. By ERNEST S. DU BRAY, M.D.	710
Leukemia: Report of an Atypical Case. By BENJAMIN GUTMANN, M.D.	718
The Relationship of Goiter to Mental Disorders. By HAROLD L. FOSS, M.D., and J. ALLEN JACKSON, M.D.	724
A Study of the Ultraviolet Absorption Spectra of Cerebrospinal Fluid—A New Test (Preliminary Report). By TAKUJI SHIONOYA, M.D.	735
Clinicopathological Study of a Series of Cases of Acute Meningo-encephalitis. By QUINTER O. GILBERT, M.D., and ADELINE E. GURD, M.D.	781
The Accuracy of the Cat Method for the Assay of Digitalis. By CHARLES C. HASKELL, M.D., and R. H. COURTNEY, M.D.	816
Paroxysmal Ventricular Tachycardia: Report of a Case Lasting One Hundred and Fifty-three Hours with Recovery. By WILLIAM B. PORTER, M.D.	821
A Case of Trypanosomiasis Treated with Tryparsamide. By HUGH J. MORGAN, M.D.	827
Syphilis as the Cause of Muscular Atrophy of Spinal Origin. By ALFRED J. OSTHEIMER, M.D., L.R.C.P. (LOND.), M.R.C.S. (ENG.), GEORGE WILSON, M.D., and N. W. WINKELMAN, M.D.	835
A Study of the Bacteriological Findings in the Lyon-Meltzer Test. By W. W. BOARDMAN, M.D.	847
The Value of Physical Signs in the Early Detection of Pulmonary Metastases. By LLOYD F. CRAVER, M.D.	852
Chronic Appendicitis and its Differential Diagnosis. By I. W. HELD, M.D.	864
Disease of the Mediastinum and its Contents. By CHARLES EDWARD HAMILTON, M.D.	888

REVIEWS

Reviews of Books.	125, 283, 438, 599, 748, 900
---------------------------	------------------------------

PROGRESS OF MEDICAL SCIENCE

Medicine	133, 291, 445, 605, 757
Surgery	135, 294, 448, 607, 761, 907
Therapeutics	137, 297, 451, 610
Pediatrics	138, 299, 453, 611, 765, 910
Dermatology and Syphilis	142, 302, 456, 614, 768
Obstetrics	145, 303, 458, 617, 914
Ophthalmology	460, 920
Gynecology	148, 306, 463, 618, 769, 918
Pathology and Bacteriology	151, 308, 465, 621, 774, 923
Hygiene and Public Health	154, 310, 467, 623, 777, 927

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JANUARY, 1924

ORIGINAL ARTICLES.

THE SIGNIFICANCE OF GLYCOSURIA IN GALL-BLADDER AND
DUCT DISEASES*

BY JOHN A. LICHTY, M.PH., M.D.,

AND

JOHN O. WOODS, A.B., M.D.,

PITTSBURGH, PA.

THE relation of pancreatic disease to diabetes mellitus is now generally accepted. The experimental observations of von Mehring and Minkowski¹ upon dogs, published in 1889, have been confirmed clinically. The credit for exploiting this discovery, the foundation for the treatment of diabetes mellitus in the human, however, is due largely to the painstaking effort and to the propaganda of education of Allen and Joslin. The idea of glycosuria being due also to disturbance of function, of liver, muscle, or kidney, and perhaps other organs and tissues has not been abandoned, but true diabetes mellitus is now definitely associated with a lesion in the pancreas or with a profound physiological disturbance of function of that organ. Glycosuria, not of pancreatic origin, is interpreted therefore in various ways, as of renal, of neurogenic, of alimentary, or of hepatic origin.

With the present knowledge of the subject, these statements may be made with very little, if any qualifications. It now only remains to determine what the specific lesion in the pancreas is,

* Read before the American Gastro-enterological Association at its Annual Meeting, April 30, 1923, Atlantic City, N. J.

¹ Diabetes Mellitus Nach Pankreas-exstirpation, Arch. f. exper. Path. u. Pharmacol., 1890, 26, 371.

and what the etiological factors of that lesion may be. When these questions are satisfactorily answered the problem of diabetes mellitus will be in a way solved. No doubt further *animal experimentation* will contribute largely to the solution of this problem, but with it must go *clinical observation* and experimentation as well.

It is for the purpose of furnishing evidence of the probable direct relation of disease of the biliary tract to diabetes mellitus that this report based upon 25 cases of glycosuria is offered.

For the past quarter of a century medical literature furnishes abundant evidence of the intimate relation of gall-bladder and duct disease to pancreatic disease and inferentially to glycosuria and true diabetes mellitus. Lancereaux² in 1899 was probably the first to call our attention to this. He was soon followed by Opie³ with his brilliant work showing by animal experimentation and clinical observation that such a relation may and does exist. After these follow the publications of many observers, all of whom up to this day recognize at least the coincidence of gall-bladder and duct disease with pancreatic disease. Mayo-Robson found disease of the pancreas in 60 per cent of all cases of stone in the common duct, and Osler says in 105 cases of pancreatitis, 45 had gall stone. Kahr reports 24 per cent of cases of pancreatic disease in 520 cases of gall stone, while the Mayo Clinic already fifteen years ago found the pancreas involved in 6 per cent of all cases operated for biliary tract disease. Some interpret the *modus operandi* of this relation in one way, others in another, and considerable controversy has arisen which it is not the purpose to enter now. It appears evident (1) that under certain anatomical conditions, be they normal, anomalous, or pathological, bile may be carried from the common duct through the ducts of Wirsung or Santorini and delivered into the body of the pancreas (Opie), (2) that the close relation of the lymphatics of the gall-bladder and the head of the pancreas may easily explain why one organ may be infected when the other carries an infection (Franke) (Sweet, J. E.)⁴ and (3) that from the present generally accepted theory of so-called focal infection it would seem passing strange if the pancreas should not be equally susceptible to infection from nearby or distant foci of infection. The question is, however, of deeper import than that of mere physical relation. It is rather more of this nature: Granting that an infected or diseased biliary tract may be responsible for disease of the pancreas, is it to be concluded in a greater or lesser number that such relation is responsible for an actual or a potential glyco-

² Traite des maladies du foie et du pancreas, Paris, Doin, 1899.

³ The Relation of Cholelithiasis to Disease of the Pancreas and to Fat Necrosis, AM. JOUR. MED. SCI., 1921, 121, 27; Acute Hemorrhagic Pancreatitis, Bull. Johns Hopkins Hosp., 1901, 12, 182.

⁴ Alvarenga Prize Essay—The Surgery of the Pancreas, Inter. Clin., 1915, 4, 293.

suria, and finally will there eventually occur a true diabetes mellitus as the result of gall-bladder and duct disease? There are reports in the literature bearing testimony to the probable relation of gall-bladder and duct disease to diabetes mellitus, basing the opinion on the fact that the glycosuria disappeared after the gall-bladder symptoms subsided. Hochhaus⁵ refers to such a case as being "the first instance of the kind on record."

Opie in the preface to the second edition of his work on the pancreas⁶ says, "Many lesions of the pancreas are unaccompanied by glycosuria, and numerous attempts have been made to define what pancreatic lesions are peculiar to diabetes. Accumulating evidence obtained by histological studies of the diseased organ has shown that diabetes mellitus accompanies those lesions which attack the ductless structure discovered by Langerhans and known as the "Islands of Langerhans." This is about the present status of our knowledge of the gross pathology of the pancreas in relation to diabetes mellitus. In the histopathology especially of the isles of Langerhans, the work of Allen, of Bensley and of others has carried us farther, and it seems that with the more recent successful attempt of Banting in separating the active principle of the isles of Langerhans and making it available for therapeutic purposes, there has occurred a new epoch in the history of diabetes mellitus, in that the treatment of the disease is now based upon conditions which have to do directly with the isles of Langerhans.

Having thus briefly referred to the advances made in the subject of diabetes mellitus, especially in relation to the biliary tract and pancreas, the collected cases forming the basis of this contribution will be discussed for the purpose of stimulating further clinical observation and research which may perhaps eventually lead to the discovery of the cause or causes of diabetes mellitus.

TABLE I.

Whole number of patients observed	23,464
Number of cases of gall-bladder and duct disease	1,474
(Of these—verified at operation or autopsy)	431
Number of cases with sugar in the urine	455
(Of these—diabetes mellitus)	373
(Of these—glycosuria)	82
Number of cases of biliary tract disease with glycosuria	25
Number of cases of biliary tract disease with diabetes mellitus (verified)	6
Number of cases of biliary tract disease with diabetes mellitus (not verified)	11
Number of cases of biliary tract disease with only glycosuria (verified)	4
Number of cases of biliary tract disease with only glycosuria (not verified)	8
Number of cases of biliary tract disease (verified) and diabetes mellitus (cured)	3

⁵ Cholelithiasis and Glycosuria, Deutsch med. Wehnschr., October, 10, 1907.

⁶ Diseases of the Pancreas, its Cause and Nature, J. B. Lippincott Co., Philadelphia, 1910.

It will be seen from this table that the number of patients seen by us in whom there was disease of the biliary tract and at the same time diabetes mellitus or glycosuria is 25. These were collected from a group of histories covering 23,464 patients. Among these patients the diagnosis of gall-bladder and duct disease was made 1474 times. Some 431 of these diagnoses were confirmed by operation or autopsy. In the same group of histories the presence of sugar in the urine was noted 455 times. Of these 455 patients having glycosuria, 373 were diagnosed as cases of true diabetes mellitus, and 82 as transient or renal diabetes, so-called. Among the 455 patients, 25 had gall-bladder and duct disease, as was stated before. An analysis of these cases is as follows: 6 were cases of true diabetes mellitus, according to all the known signs and symptoms of that disease, and were proven at operation or autopsy to have a diseased biliary tract; 11 more were as truly diabetes mellitus, but none of these were operated upon or came to autopsy. Hence, the diagnosis of biliary tract disease must be in doubt. However, except for this, on account of the history and course of the disease, the diagnosis of biliary tract was the only reasonable one. Of the 6 cases of true diabetes mellitus and verified biliary tract disease, 3 after operation apparently recovered from their diabetes mellitus, as well as from the gall-bladder and duct disease. These deserve particular consideration.

Case Reports. CASE I.—T. S. H., No. 15,128, aged fifty-eight years, a business man, was first seen by one of us (Lichty) April 11, 1916, when he complained of periodical attacks of epigastric pain extending over five years. These attacks were accompanied by nausea, vomiting, and chilly sensations with a temperature at one time as high as 101° F. He had no gastro-intestinal symptoms of consequence between the attacks. Sugar was found in the urine eighteen months previously on a routine examination; since that time he observed polyuria at various times. The carbohydrates had been eliminated from his diet, but sugar was still present. A loss of 30 pounds in weight was noted in the preceding five years.

The outstanding points in the physical examination were slight icterus of the conjunctivæ, a blood-pressure of 120-90, and an occasional ectopic beat. No valvular lesion was noted.

The laboratory examinations of the blood and gastric contents were normal. The urine was 1028 in specific gravity with 0.41 per cent glucose in a twenty-four-hour specimen; the blood sugar was 0.26 mg. per 100 cc blood. With regulation of the diet the patient became sugar-free and the blood sugar 0.23. He was operated upon two weeks later, after the blood sugar was lower, by Dr. J. J. Buchanan at the Mercy Hospital.

The operative findings were a chronically infected and thickened gall-bladder with a number of stones in the gall-bladder and one

in the common duct. The pancreas presented no gross anatomical lesions. Both the gall-bladder and the common duct were drained. Following the operation, no sugar was found in the urine and the blood sugar came to the normal on a regular diet.

This case presented a very severe infection of the gall-bladder and biliary tract and the postoperative convalescence was therefore quite protracted. A letter from his family physician two months later reported that the sugar returned occasionally on a full diet until he had thoroughly convalesced.

All trace of the patient was then lost until April 10, 1921, when he returned to the hospital with cough, dyspnea and edema of the legs and a general cardiac breakdown. Physical findings and electrocardiographic tracings at this time established the diagnosis of a chronic myocarditis with a marked loss of reserve. Sugar had not been present in the urine for three to four years to his knowledge and none was found during a stay of two weeks at the hospital. The highest blood-sugar finding was 0.11* on a full diet. He recovered compensation before leaving the hospital, but died six months later, death being due to a recurrence of the cardiac decompensation.

CASE II.—B. T. S., No. 22,168, aged forty-nine years, a railroad engineer, first consulted us November 11, 1921, when he complained of pains over the lower abdomen for a month or more referred upward to the chest and back. He spoke of three severe attacks of abdominal pain, the first twenty-five years ago following typhoid fever, the second fifteen years ago followed by symptoms of diabetes mellitus, and the last two weeks before he came to our observation. These attacks persisted for one to two days, were accompanied by nausea and vomiting and required hypodermics of morphine for relief. No jaundice had been observed. Sugar had been present in the urine periodically for fifteen years; at times polydipsia and polyuria were present. During the above period of fifteen years he had progressively lost about 35 to 40 pounds in weight. The physical examination showed nothing of note other than slight tenderness in the right upper abdomen.

The twenty-four-hour specimen of urine was 3500 cc in volume, specific gravity 1015, and a slight trace of sugar. The gastric analysis and blood count were normal. The blood sugar was 0.20. The patient was given a diet eliminating the starches. Two weeks later the attacks of pain were still present and a trace of sugar was still present in the urine. Hospital treatment was advised.

A roentgen-ray of the gastro-intestinal tract was negative; except for a defective filling of the right side of the duodenal cap. The Lyon test showed "A" and "C" biles present, but no "B" bile. Because of the history and the rather definite train of symptoms, a

* Blood-sugar findings are expressed as percentages.

diagnosis of gall stones with diabetes mellitus was made, and operation advised.

At the operation, by Dr. O. C. Gaub, at the Columbia Hospital, the gall-bladder was found to be thick, contracted, and filled with stones; the pancreas showed no demonstrable pathology. A cholecystectomy and appendectomy were done.

Five days after operation 1 per cent sugar was found in the urine and the blood sugar was 0.22. The sugar remained in the urine for about a week and then disappeared with restriction of the carbohydrates in the diet. On discharge from the hospital one month after operation the blood sugar was 0.13 and the urine showed no sugar.

The patient was seen from time to time up to November 2, 1922. During that period, he felt entirely well and was eating a general diet. The urine was examined on his various visits to the office and never showed any sugar. The blood sugar was taken on all occasions and varied from 0.14 to 0.17 on a general diet. (May 31, 1923, the urine was sugar-free and the blood sugar was 0.12 on a general diet.)

CASE III.—O. A. W., No. 23,245, aged forty-seven years, a shop foreman, was seen by us November 4, 1922, when he complained of a dull aching in the epigastrium for the previous five months. This aching occurred about two to three hours after meals and was usually localized in the epigastrium. It was relieved by eating and also by a glass of milk or soda, but was worse after acid foods. One year ago he had a severe attack of epigastric pain with nausea, for which he was given a hypodermic of morphine and was relieved in about an hour. No jaundice had been observed.

For four to five months before coming to the office his strength had not been normal and during that period he had also lost 20 pounds in weight. His family physician had recently found sugar in the urine on several occasions. The physical examination was negative except for slight tenderness in the epigastrium.

The urine examination showed a slight trace of sugar with the blood sugar 0.13 mg. per 100 cc blood, and the gastric analysis was free HCl 76, combined 20, total 96, with no blood. The blood count was normal and the Wassermann negative. The roentgenogram of the gastro-intestinal tract showed the stomach normal in size, shape, position, and motility, but the outline of the duodenal cap on the right was irregular, possibly due to adhesions. With the Lyon test "A" and "C" biles were present, but no "B" bile. Over a period of about ten days traces of sugar were seen in about half the daily twenty-four-hour collections. With the glucose-tolerance test the fasting blood sugar was 0.13; the blood sugar at forty-five minutes 0.20, and at two hours 0.30; sugar was found in both urinary specimens at the forty-five minute period and again in two

hours. A diagnosis of chronic cholecystitis with secondary glycosuria was made at this time and operation advised.

A laparotomy, done by Dr. John W. Dixon, at the Columbia Hospital on November 18, 1922, disclosed a greatly distended gall-bladder filled with stones and surrounded by dense adhesions from the duodenum and stomach to the liver; the pancreas showed no definite pathology. A cholecystectomy was performed.

Following operation twenty-four-hour specimens of urine were taken daily and again sugar was found in about one-half the specimens, usually in small amounts; the blood sugar was taken every four days during that period and varied from 0.17 to 0.20. On discharge from the hospital on December 9, 1922, the blood sugar was 0.18 and the urine had been free from sugar for two days. A restricted diet list was prescribed and the patient advised to report later for further directions and regulation of the diet.

Since that time he has been seen at intervals of two to four weeks, the last consultation being on April 10, 1923. During that period the blood sugar has varied from 0.09 to 0.13 on various examinations and sugar has never been found in the urine. He now takes a general diet and is free from epigastric discomfort of any kind.

These 3 cases were apparently cured of their diabetes mellitus as a result of an operation upon the biliary tract. The number is small compared with the number of cases seen having both conditions. It might be added that the remaining patients with true diabetes, 11 in all, seemed more amenable to dietetic treatment than the average case. Also the remaining 11 cases of glycosuria only were easily cleared of their sugar, in fact in some of them it had appeared only once or twice (as seen in Table II).

In an analysis of these cases it is obviously unwise to draw any definite conclusions. Insofar as the incidence of the two conditions in the same patient is concerned, it could be accounted for entirely from the standpoint of coincidence. In fact, the chance, according to Prof. Raymond Pearl, of the Department of Biometry and Vital Statistics of the School of Hygiene and Public Health, Johns Hopkins, of the coincidence alone is higher than that of 25 cases of diabetes mellitus among 14,747 cases of gall-bladder and duct disease. We were favored with an opinion from Prof. Pearl which is as follows: "On the basis of your experience, the probability that one of your patients will have gall-bladder and duct disease is .062820. The probability that one of your patients will have glycosuria is .019349. The probability that one of your patients will have *by chance alone* both of these conditions together in the same individual is .001216, which means that, on the basis of a total experience of 23,464, it would be expected that 28.5 individuals would purely as a result of chance have both of these conditions associated together in the same individual. Actually, you found 25 individuals who had both gall-bladder disease and glycosuria.

From this I conclude that you have no basis for asserting that in your experience the association of these two diseases is either more or less frequent than would be expected from a chance association.

"Now to consider the association of diabetes mellitus with gall-bladder disease, the case is as follows: The probability of gall-bladder disease is as before .062820. The probability of diabetes mellitus in your experience is .015854. The probability of gall-bladder disease and diabetes mellitus in the same patient on the basis of chance alone is .000996, which means that there would be expected, on an experience of 23,464, 23.7 patients in which these two conditions were associated together purely as a result of chance. Actually, the number you found was 14. This indicates that this combination of diabetes mellitus and gall-bladder diseases occurs only a little more than one-half as frequently as would be expected from chance alone. This difference between observed and expected is to be regarded, I think, as quite probably significant."

Therefore if the object of our thesis were only to furnish evidence to the proposition that disease of the biliary tract is a cause of diabetes mellitus, we would be compelled to conclude, according to our statistics, that the case is not proven. According to our experience and thinking however, as stated before, the problem is deeper than this and cannot be entirely solved on the basis of statistics.

One of us (Lichty) recalls a patient some fifteen years ago who, while convalescing from typhoid fever, was suddenly seized with severe pain in the right upper quadrant. The temperature, which had been normal for a time, now ran a course like that of a relapse. The patient became jaundiced and in a few weeks developed a regular Charcot's intermittent fever. There was finally a dull, heavy pain in the left lumbar region with a fluctuating swelling to the outer edge of the left lumbar muscle. This swelling was incised and, besides a free flow of pus, pancreatic tissue was recovered from the pus cavity which appeared to be retroperitoneal. The patient presented at no time any evidence of pancreatic insufficiency, excepting rapid emaciation and profound weakness. At no time was any sugar found in the urine. At the autopsy the entire biliary tract was distended with pus, and the pancreas was almost entirely destroyed. What was left of the tail of the pancreas lay in the wound of the operation. Evidently the pancreas may carry the most extensive infection and destructive pathology and yet maintain its function, especially that part of its function related to carbohydrate metabolism. This is, of course, not a new idea. It is also well known that the proportion of isles of Langerhans to external secreting tissue increases in a very definite ratio toward the tail of the pancreas. Hence, extensive lesions may occur at the head of the pancreas, for example, in the so-called "acute angle" of acute infection without disturbing carbohydrate metab-

TABLE II.—CASES OF BILIARY TRACT DISEASE ASSOCIATED WITH GLYCOSURIA.—DIABETIC SYMPTOMS.

Serial number.	Case number.	Name.	Age.	Sex.	Occupation.	Duration.	Thirst.	Polyuria.	Weakness.	Loss of weight.	Skin lesion.	Glycosuria (per cent).	Blood sugar (highest).
1	22,168	B. T. S.	49	M.	Eng.	15 yrs.	+	+	+	+	○	Tr.	0.20
2	23,245	O. A. W.	47	M.	B. M. ¹	1 mo.	○	○	+	+	○	Tr.	0.17
3	15,128	T. S. H.	58	M.	B. M.	1 yr.	+	+	+	+	○	0.5	0.26
4	22,761	B. B.	67	F.	H. W. ²	6 mos.	○	○	+	○	+	5.0	0.22
5	23,588	R. L.	48	F.	H. W.	6 mos.	+	+	+	+	○	1.2	0.30
6	7,944	K. M.	64	F.	H. W.	2 mos.	+	+	+	+	+	6.0	
7	8,261	W. S. V.	44	F.	H. W.	6 mos.	○	○	+	○	○	1.0	
8	11,192	R. H. G.	58	F.	H. W.	6 wks.	○	○	○	○	+	Tr.	
9	7,845	H. L. T.	50	F.	H. W.	○	○	○	○	○	Tr.	
10	14,185	M. O.	47	M.	Lab. ³	○	○	+	+	○	Tr.	
11	23,618	R. L. S.	30	M.	Phy.	3 yrs.	○	+	○	○	○	Tr.	0.17
12	6,931	J. S.	62	F.	H. W.	3 yrs.	○	○	○	+	+	1.3	0.24
13	8,432	R. T. R.	40	F.	H. W.	1 yr.	○	○	+	+	○	6.0	0.4
14	6,800	W. S. B.	58	F.	H. W.	2 yrs.	○	○	○	○	+	1.5	
15	23,316	A. H.	60	F.	H. W.	10 yrs.	+	+	+	+	○	1.0	0.22
16	21,167	H. C. C.	50	F.	H. W.	2 yrs.	+	+	+	+	+	1.6	0.16
17	20,684	C. A. S.	34	F.	H. W.	6 mos.	+	+	○	○	○	1.5	
18	15,051	A. D.	46	F.	H. W.	2 wks.	○	○	○	+	○	1.5	0.14
19	19,476	E. S.	67	F.	H. W.	2 yrs.	+	+	+	+	+	0.1	0.21
20	20,297	M. K.	62	F.	H. W.	2 yrs.	+	+	+	+	○	1.0	0.18
21	23,181	K. B. C.	50	F.	H. W.	4 mos.	○	○	○	○	○	Tr.	0.16
22	18,913	J. F. S.	55	M.	Lab.	6 mos.	○	○	○	+	○	Tr.	
23	23,477	J. J. H.	42	F.	H. W.	1 mo.	○	○	○	○	○	Tr.	0.11
24	15,178	H. Z.	51	F.	H. W.	1 wk.	○	○	○	○	○	Tr.	
25	23,478	J. S.	70	M.	Lab.	2 mos.	○	○	○	○	○	Tr.	

¹ B. M.—Business man.

² H. W.—Housewife.

³ Lab.—Laborer.

TABLE II.—Continued.—GALL-BLADDER SYMPTOMS.

Serial number.	Duration.	Attacks.	Pain.	Nausea.	Vomiting.	Jaundice.	Fever.	Tenderness.	Blood-pressure.	Gastric.	Treatment.
1	25 yrs.	3	Epig.	○	○	○	○	Epig.	120-75	F. C. T. ²	
2	1 yr.	1	Epig.	+	○	○	○	Epig.	156-94	20-16-36	Op.
3	5 yrs.	Many	G. B. ¹	+	+	+	+	0	170-100	76-20-96	Op.
4	5 yrs.	3	G. B.	○	○	○	○	0	172-85	12-8-28	Op.
5	14 yrs.	Many	G. B.	+	+	○	○	G. B.	160-90	Pre. Op.
6	7 yrs.	1	Epig.	+	+	+	+	G. B.	210-70	30-10-40	Pre. Op.
7	6 mos.	7	Epig.	+	+	○	+	G. B.	132-80	Pre. Op.
8	8 yrs.	Many	G. B.	+	+	○	+	G. B.	140-80	37-17-68	Pre. Op.
9	3 yrs.	Many	G. B.	+	+	+	+	G. B.	160-80	28-14-56	Pre. Op.
10	5 mos.	0	Epig.	○	○	+	○	Epig.	120-84	46-22-84	0
11	6 mos.	0	0	+	○	+	+	Appdx.	120-80	Achylia	Op.
12	6 mos.	2	G. B.	+	○	○	○	G. B.	195-130	20-20-40	Med.
13	6 yrs.	4	G. B.	+	○	○	○	G. B.	160-80	Med.
14	5 yrs.	Many	G. B.	+	○	○	○	G. B.	160-80	14-30-58	Med.
15	1 yr.	0	0	+	+	○	○	G. B.	220-110	Med.
16	6 yrs.	2	G. B.	+	+	○	○	G. B.	214-116	0
17	2 yrs.	Many	Epig.	+	+	○	○	G. B.	140-90	36-30-72	Med.
18	2 yrs.	2	G. B.	+	○	○	○	0	150-90	32-14-52	Med.
19	2 yrs.	0	Epig.	○	○	○	○	G. B.	145-80	Med.
20	2 yrs.	0	Epig.	+	+	○	○	G. B.	150-90	10-20-35	Med.
21	2 yrs.	4	Epig.	+	+	○	+	G. B.	144-74	Achylia	Med.
22	9 yrs.	Many	Epig.	+	+	○	○	G. B.	160-105	82-10-96	Med.
23	4 yrs.	0	Epig.	+	○	+	○	G. B.	120-80	Med.
24	1 wk.	0	0	+	○	+	○	G. B.	208-130	40-20-68	Med.
25	2 mos.	2	Epig.	+	○	○	○	G. B.	220-120	30-20-50	Med.

¹ G. B.—Gall-bladder.

² F.—Free HCl; C.—Combined; T.—Total.

olism in the least. The relation of the lymphatics, as shown by Franke, as well as the anatomical relation of the ducts, as described by Sweet in his Alvarenga Prize Essay, shows plainly how the isles of Langerhans are fairly protected from invasion from the biliary tract. With the present tendency to the liberal interpretation of the effects of focal infection, and with the renewal of interest in diabetes mellitus, other foci of infection besides the gall-bladder and ducts have received consideration. In such cases the route of invasion is very likely that of the blood stream which may of course also be the route as well of the lymphatics when the biliary tract is the focus of infection. In our own experience that of the tonsils is noteworthy. We have not collected our statistics bearing on this phase recently, but we do not recall any such striking results from tonsillectomies as we have from cholecystostomies or cholecystectomies. We can only say that patients having diabetes mellitus and diseased tonsils do better after a tonsillectomy.

The indications for surgery in gall-bladder and duct diseases *per se* are fairly well defined. It is our opinion, however, based upon a limited experience that (1) on account of the possibility of gall-bladder and duct disease being later complicated by diabetes mellitus, and on account of the conceded increased danger of operation after such a complication has occurred, there is an added indication for prompt surgery in all biliary tract disease; (2) on account of the apparent cure of diabetes mellitus (a heretofore supposedly incurable disease) as found in our own limited experience, we believe a certain operative risk is justifiable in cases of diabetes mellitus giving reasonable evidence of gall-bladder and duct disease; and (3) the urine and the blood should receive a more careful and purposeful study in all cases of suspected gall-bladder and duct disease.

THE SPLEEN AND DIGESTION. STUDY IV. THE SPLEEN AND BILIARY SECRETION; THE REACTION IN BILE-PIGMENT SECRETION FOLLOWING SPLENECTOMY.

BY WILLIAM DEP. INLOW, M.D.,

FELLOW IN SURGERY, DIVISION OF EXPERIMENTAL SURGERY AND PATHOLOGY, THE MAYO FOUNDATION, ROCHESTER, MINNESOTA.

THE concept that the spleen influences the amount of bile pigment secreted by the liver is one that has received common credence. However, the amount of experimental work on the problem of an interrelationship between the spleen and the secretion of bile has been less than that carried out with regard to the relation of the spleen to gastric and pancreatic secretions. The present study was originally undertaken from the viewpoint of the effect of splenec-

tomy on the secretion of bile as a digestive fluid; however, the chief significance of the results is in the data offered with regard to the secretion of bile pigment. Data are also presented to show the effects of various types of diet on the secretion of bile, before and after splenectomy.

Review of the Literature. From the time of Galen, a functional relationship between the spleen and the liver has been postulated. According to Gray, early in the eighteenth century, Lieutaud definitely assigned to the spleen a functional influence on the secretion of bile, proposing that "the blood by its retardation in the spleen, will be rendered thicker, and consequently more fit for the secretion of the bile; and that when the stomach is full, it will be pushed toward the liver, which receives more blood during digestion, and separates, consequently, more bile." To quote Gray further: "The immortal Cuvier attempted to elucidate the function of the spleen by the aid of comparative anatomy, he being the first author who treated to any extent of the structure of this organ in animals. He indirectly states the spleen to have two functions. Thus, the spleen has on the one hand some immediate relation with the secretion of the bile, and on the other, some indirect relation with that of the digestive juices, or of the commencement of the intestinal canal. These functions he deduced more particularly from consideration of the arrangement of the vessels of the organ. In the oviparous vertebrates he observes that the arteries of the spleen being derived from those which supply the stomach, or commencement of the intestinal canal, there result certain relations in the distribution of blood to these different viscera, probably of great importance with reference to the function of the spleen; so that the easier the access of the blood to the spleen, the more difficult it is to the arteries immediately in relation with it; consequently the more blood will the spleen turn to its own purposes, and the less abundant will be the gastric juice; while, on the other hand, these conditions will be reversed, when the access of the blood to the stomach is easier, and that to the spleen more difficult. It was from these facts that he deduced one of the functions of this organ to be that of having some indirect relation with the secretion of the gastric juices, whilst the fact of the splenic vein forming in many animals the most important branch of the vena portæ, led him to believe that it had some immediate relation with the secretion of the bile."

Ponfick, in 1883, considered that the spleen disintegrated erythrocytes, and suggested that bile pigment was derived from hemoglobin set free in this organ and carried to the liver through the portal circulation. This theory was supported by Pugliese and Luzzatti in a study of the effect of hemolytic poisons on splenectomized animals. Pugliese, in 1899, investigated the effect of splenectomy on the secretion of bile in two dogs with biliary fistulas. He found

that the quantity, density, dry residue, and alcoholic extract of the bile were not modified by removal of the spleen; however, the amount of bile pigment secreted was diminished more than one-half. In a further communication he confirmed these researches, and reported that the amount of ash for each 100 cc of bile, and the amount of sulphur (that is, bile acid) remained unchanged by splenectomy. He concluded, therefore, that splenectomized dogs secrete bile less rich in biliary pigment, but with normal content of bile acid. In a later investigation (1913), he found a moderate increase in the amount of bile secreted after splenectomy with a considerable reduction in the amount of iron content. (The average iron content for each 100 cc fell from 2.25 mg. to 1.63 mg.).

Likewise, Charrin and Moussu made fistulæ into the fundus of the gall-bladder in dogs, and studied the effect of splenectomy. They found that three or four days after the removal of the spleen, the bile became more dilute and partially decolorized, and that it contained relatively less organic material (pigments, bile salts, pseudomucin, cholesterol, lecithin, neutral fats, soaps, urea). They concluded that the spleen exercises on the liver an undeniable action which, aside from hematopoietic, antitoxic considerations, consists essentially of a biligenic function. Their results differed from those of Pugliese merely in the obtaining of a diminution in the dry extract of bile after splenectomy.

Paulesco, in 1906, criticised the methods previously used. He maintained that the bile secured from a fistula of the gall-bladder is not normal, and not of constant composition, that the amounts of pigments and of salts are less than when bile is not excluded from the intestine, and the digestive process is disturbed. He carried on three series of experiments: Analyses of bile from the gall-bladder of normal dogs; similar analyses of bile from dogs whose spleens had been removed seventeen to one hundred and fifty-eight days before; and examination of the bile from 3 dogs before and after splenectomy, the bile having been collected by puncturing the gall-bladder. His conclusions were: (1) that the vesicular bile of splenectomized dogs does not differ notably from that of normal dogs with their spleens intact; and (2) that there is no marked or constant difference between the composition of the bile before and after splenectomy; therefore, there is no manifest relation between the functioning of the spleen and the secretion of bile by the liver.

Pearce says, "In regard to the decreased tendency to hemoglobinuria and jaundice after the administration of hemolytic agents (in splenectomized animals), we offer experimental evidence to indicate that (1) absence of the spleen does not prevent the secretion of bile; (2) the spleen does not influence the transformation of free hemoglobin into bile pigment; and (3) that fresh splenic extracts have no demonstrable action *in vitro*."

Goto, in 1917, found in 4 dogs with anastomoses between the

bile duct and the right ureter, an output of bile pigment in the urine under normal conditions, varying between 0.0618 and 0.0678 gm. daily. There was definite evidence of a decrease in the elimination of bile pigment after splenectomy, and also when a hemolytic agent was administered. These observations appeared to show that the absence of the spleen definitely influences the formation of bile pigment.

The most recent and extensive studies of bile pigment metabolism are those of Whipple and Hooper. They draw many important conclusions with regard to the relation of the spleen to biliary secretion. The following is quoted from the summaries of various communications. "Splenectomy causes many interesting reactions in bile-fistula dogs, but it does not influence the output of bile pigments under normal conditions. . . . Splenectomy has no effect on the secretion of bile pigments in dogs ingesting blood or bile. . . . The Eck-fistula liver secretes much less bile pigment than the normal liver. . . . Splenectomy added to the combined bile and Eck fistula does not essentially modify the result. . . . Splenectomy added to a simple bile fistula modifies in no way the secretion of bile pigments in the bile. A large number of experiments control this statement. Hemoglobin injected intravenously gives no constant increase in the output of pigments in the bile. Splenectomy does not modify this reaction. . . . Dogs with bile fistulæ, anemia, and an added splenectomy may show some remarkable deviations from the control experiments. Experimental anemia in these bile-fistula-splenectomy dogs may give a very remarkable reaction; periods of spontaneous icterus, blood destruction and high bile pigment output may alternate with periods of regeneration and low bile pigment output without any demonstrable cause. An interaction of the liver and spleen in the construction, as well as in the destruction of the hemoglobin and red-cell stroma may be indicated by these experiments. Regeneration of red cells with consequent recovery from the experimental anemia is very greatly prolonged, and may occupy months in the splenectomy experiments as compared with weeks in the simple bile-fistula experiments without splenectomy. The color index may remain uniformly high during this long period of blood regeneration in the splenectomy experiments. The output of bile pigments may average considerably above normal, and we may suspect an overproduction of blood and bile pigments with perhaps a deficiency of red-corpuscle stroma." Thus it is seen that the results and conclusions of various investigators in this field vary greatly.

Experimental Methods. Observations were made on 4 dogs, weighing, on the average, about 8 kg., with permanent biliary fistulæ. These fistulæ were made according to the technic described by Mann, except that at the first stage of the procedure, the gall-bladder was removed. This technic consists essentially of the trans-

plantation of the duodenum under the skin at a primary operation (done under ether anesthesia and employing sterile technic), and the severance of the common bile duct with its transference to the outside at a second operation a few weeks later, thus establishing a permanent fistula into the common bile duct.

The animals, between observations, were kept in cages and not exercised, and were given mixed food consisting of raw meat, lard, milk and bread. They were permitted to eat as much of this mixture as they desired. Water was given freely up to five hours before the beginning of each period of collection, and then withheld. Three types of procedure were carried on: (1) The bile was collected after the animal had fasted for eighteen hours; (2) after withdrawal of food for five hours, the animal was fed on various types of foodstuffs (raw, lean meat, lard, sugar and milk) in equivalent caloric values for each kilogram of body weight (on the average a secretory meal of 280 calories for an 8 kg. dog was given, an ordinary caloric intake sufficient for one day) two hours before the beginning of the collection; and (3) after withdrawal of food for five hours, the animal was given secretory meals of the foodstuffs mentioned two hours after the beginning of the collection of bile.

The bile was collected by introducing a rubber catheter into the common bile duct. After a preliminary drainage of fifteen minutes, the amounts of bile secreted were measured at intervals of two hours. Periods of six hours were used for the collection of bile, as employed by Whipple and Hooper (for comparison of this six-hour period with twenty-four hour periods see Wisner and Whipple).

Determinations of bile pigment content were made colorimetrically after the method of Whipple and Hooper. A Hellige colorimeter was used, and the standard wedge of copper sulphate was graduated into milligrams of bilirubin by comparison with different dilutions of pure bilirubin (Pfanstiehl). The taurocholic acid of the dog's bile was analyzed by the method of Foster (hydrolysis of taurocholic and taurocholic acids by sodium hydroxid into taurin and cholic and choleic acids, and quantitative determination of the ammonia given off by the taurin in the Van Slyke amino-nitrogen apparatus). Several specimens of bile were tested for cholesterol, but none was found.

Blood counts were made at weekly intervals, usually about two hours after the giving of food, and hence during the period of digestion, except in instances of fasting. The hemoglobin was determined by the Dare hemoglobinometer. A record of the body weight also was kept.

After the establishment of a norm for the amount of secretion, and content of pigment and bile acid, splenectomy was performed on 3 dogs and the subsequent effect on biliary secretion noted. All operative procedures were conducted under ether anesthesia with the employment of sterile technic.

Experimental Data. PROTOCOLS.* Dog E237.—A male mongrel in good condition, weighing 12.3 kg. January 26, 1921, the duodenum was transplanted under the skin and the gall-bladder removed. April 14, a permanent biliary fistula was established. The animal did well until May 9, when marked anorexia rapidly appeared and it lost weight. Death occurred May 16. At necropsy the common bile duct was found dilated to four times normal size. Death was probably due to the loss of bile.

TABLE I.—DETERMINATIONS OF NORMAL BILIARY SECRETION OF DOG E237. FASTED EIGHTEEN HOURS, THEN FED 50 GM. OF LARD TWO HOURS AFTER BEGINNING THE EXPERIMENT.

	Secretion, cc.				Bile pigment, mg.				Blood count.			Wt.
	First two hours.	Second two hours.	Third two hours.	Total.	First two hours.	Last four hours.	Total.	Each kilogram for each six hours.	Hemoglobin, per cent.	Erythrocytes (millions).	Leukocytes (thousands).	Kilograms.
1921.												
April 27	15.7	12.4	10.5	38.6	10.2	16.0	26.2	10.0
30	17.2	15.1	17.3	49.6	6.9	13.8	20.7	10.3
May 4	18.4	18.3	17.0	53.7	9.6	22.9	32.5	9.7
7	8.1	23.2	16.3	47.6	6.9	31.6	38.5	..	83	6.05	20.7	9.8
Average	47.4	29.5	2.96	9.95

Dog E236.—A male mongrel in good condition, weighing 11.1 kg. April 6, 1921, the duodenum was transplanted without removal of the gall-bladder. The wound became infected, but healed. May 18, the gall-bladder was removed and a fistula of the common bile duct established. June 8, splenectomy was performed. A slight perisplenitis was present. The animal remained in good condition until October 5, when in the course of another experimental inquiry, sudden death occurred after the injection intravenously of 20 cc of the animal's own laked blood. At necropsy the liver was found in good condition. The common bile duct was dilated.

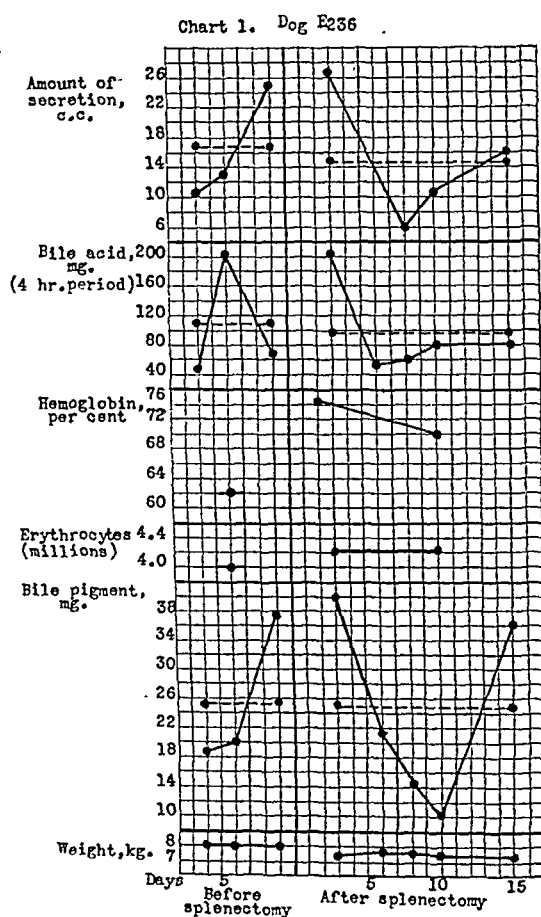
Dog E335.—A male terrier in good condition, weighing 8.7 kg. February 25, 1921, the duodenum was transplanted and the gall-bladder removed. April 14, a biliary fistula was established, and May 25, the spleen was removed. The animal remained in good condition for several months. Death occurred October 5, apparently from loss of biliary secretion. At necropsy no marked findings were present. The biliary tract was somewhat dilated. The liver appeared normal.

* It should be emphasized that with the exception of Dog E237 all animals were in excellent condition during the period of time the data in this study were obtained, and for many weeks after the completion of these observations.

TABLE II.—DETERMINATIONS OF BILIARY SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG E236. FASTED EIGHTEEN HOURS, THEN FED 35 GM. OF LARD, TWO HOURS AFTER BEGINNING THE EXPERIMENT.

1921.	Secretion, cc.				Bile pigment, mg.				Taurocholic acid, mg.				Blood count.			Weight. Kilograms.
	First two hours.	Second two hours.	Third two hours.	Total.	First two hours.	Last four hours.	Total.	Each kilogram for each six hours.	First two hours.	Last four hours.	Total.	Each kilogram for each six hours.	Hemoglobin, per cent.	Erythrocytes (millions).	Leukocytes (thousands).	
June 2 . . .	3.3	4.0	3.6	10.9	4.8	14.4	19.2	..	20.5	50.9	62	4.00	22.1	8.00
4 . . .	4.8	4.2	4.3	13.3	4.7	15.5	20.2	..	63.5	206.0	8.00
7 . . .	8.4	9.6	7.2	25.2	8.2	28.9	37.1	3.19	42.0	71.6	151.5	18.9
Av.	16.5	25.5	Splenectomy, June 8.	..	109.5
June 11 . . .	8.3	8.8	10.0	27.1	11.8	28.2	40.0	..	78.9	205.4	75	4.22	25.2	7.60
14 . . .	5.4	3.2	4.2	12.8	6.5	15.3	21.8	..	56.5	58.0	7.80
16 . . .	1.6	2.2	2.2	6.0	3.6	11.2	14.8	62.5	7.60
18 . . .	4.3	3.8	3.8	10.6	2.6	8.0	10.6	..	53.1	83.9	70	4.24	11.2	7.50
23 . . .	40.0	6.2	6.0	16.2	9.8	26.2	36.0	..	22.6	81.7	7.20
Av.	14.9	24.8	3.27	58.8	98.7	157.5	20.9	7.54

Dog E168.—A male mongrel, weighing 10.7 kg. December 28, 1920, the duodenum was transplanted, and the gall-bladder removed. February 23, 1921, a biliary fistula was established, and March 23, the spleen was removed. After finishing this series of experiments, the animal was used from August 20 to September 7, for the study of bile pressure. Later laked blood was injected. This made the animal acutely ill, but he recovered. Death occurred suddenly October 14. At necropsy no cause for death could be found, except the presence of the long continued biliary fistula. There was marked emaciation. Grossly, the liver appeared normal.

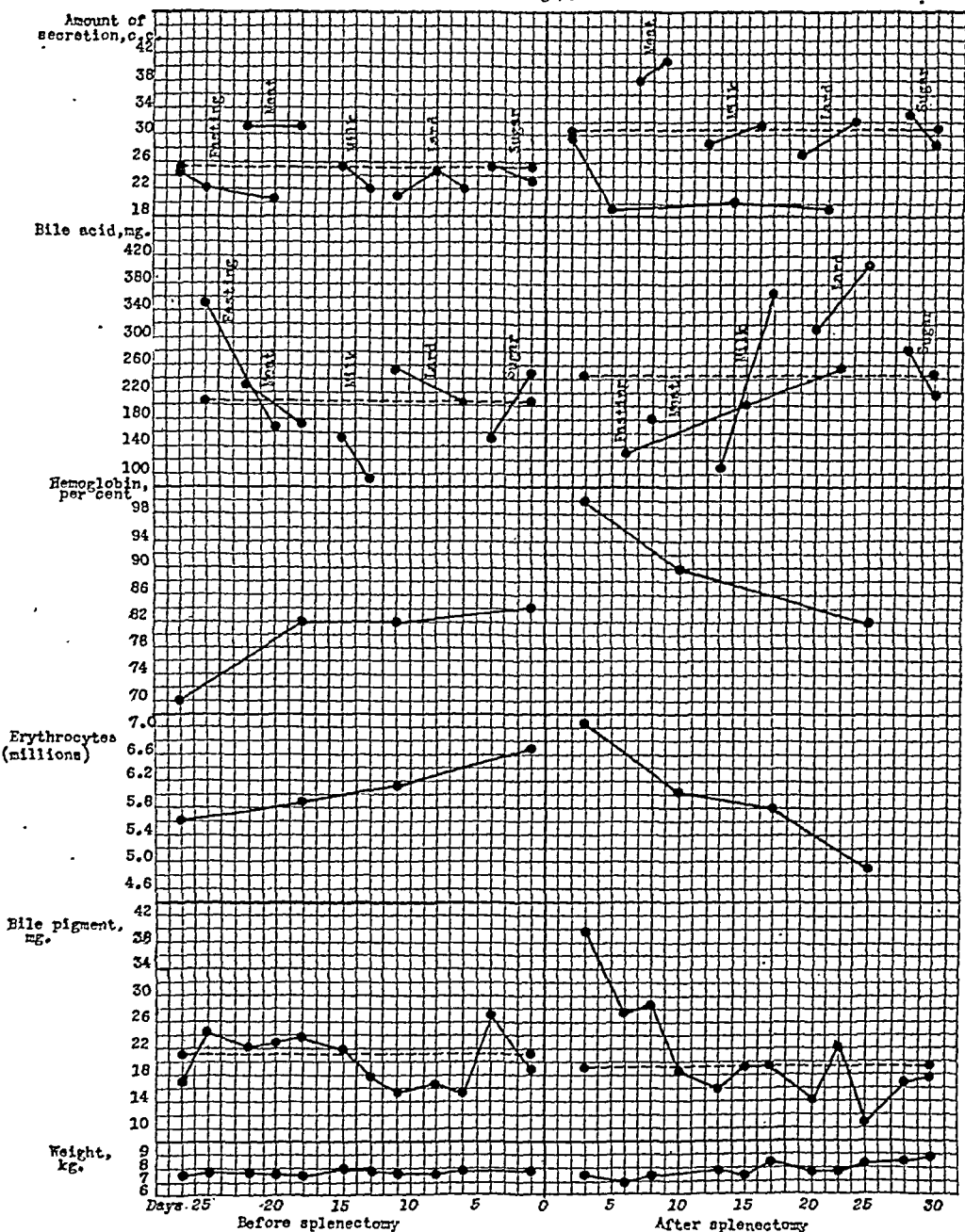


Review and Discussion of Experimental Data. From the experimental data presented, it seems that certain general conclusions can be drawn, both with regard to the normal secretion of bile, and the effect of splenectomy; however, there are certain phenomena which, because of the irregularity of their appearance, do not permit definite deductions.

THE AMOUNT OF BILIARY SECRETION. The amount of bile secreted normally for each unit of time in any one animal was fairly uniform. The uniformity was most marked in the two-hour periods taken on any one day. The fluctuations were greater when

the findings of different days were compared. The differences due to diet were not striking, but were definite. The smallest amount of secretion was noted in the fasting animal. When milk, lard,

Chart 2. Dog E335



and sugar and water were given, the amount of secretion was only slightly increased; when meat was given the increase was quite marked. Such increase was most evident when the animal was fed two hours after beginning the collection, in which case it was noted

that the amount of secretion for the next two periods of two hours was doubled. The amount of bile secreted may vary greatly in different dogs. Much less was obtained in my experiments than was obtained by Whipple and Hooper during a similar six-hour period.

After splenectomy, there were certain very definite changes in the amount of biliary secretion. In the fasting animal, the amount was slightly increased during the first few days; later it fell somewhat below normal. With the giving of food, the amount of secretion was increased about one-fourth above its presplenectomy value; this was most constant in the case of meat feeding. The fluctuations in the amount of secretion from day to day were greater after splenectomy than before, probably because of circulatory changes in the branches of the celiac axis, and in the portal system, incident to the ligation of the splenic artery and vein. The theory of the regulatory influence of the spleen in this circulatory system is supported by these findings.

THE BILE ACID. The amount of bile acid fluctuated greatly from day to day. The amount secreted seemed least during fasting, and greatest after meals of lard, and of meat, but these reactions were not constant. The output of bile acid varied to some extent with the amount of bile secreted; a profuse secretion of bile was accompanied by a high total content of bile acid, and *vice versa*. There seemed to be no relation between the output of bile pigment and that of bile acid. The amounts of taurocholic acid obtained were less than those reported by Foster, and Hooper and Whipple, and the fluctuations greater. Removal of the spleen did not cause any definite and constant changes in the output of bile acid.

THE BLOOD. The hemoglobin determinations and the erythrocyte counts showed the typical postsplenectomy reaction of anemia, as described by Pearce and collaborators.¹⁸ The percentage of hemoglobin was increased on the third day after the operation, and removal of the spleen; it then decreased below normal, reached its lowest point two or three weeks after splenectomy, and then gradually returned to normal. Subsequent fluctuations occurred, but they were not marked. The erythrocyte count reacted similarly, except that the drop was less acute; for example, in Chart 3, the lowest count was made five weeks after the removal of the spleen, and later recovered.

THE SECRETION OF BILE PIGMENT. The output of bile pigment was remarkably uniform. The values for each two-hour period on the same day varied but little; the differences from day to day were greater. There seemed to be a definite relationship between the amount of bile secreted and its unit concentration in bile pigment (figures not included in tables), so that a profuse secretion had a low concentration of pigment and *vice versa*; by this mechanism the total amount of pigment secreted remained about uniform. The output of bile pigment in these experiments was approximately

TABLE III.—DETERMINATIONS OF BILIARY SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG E335. FASTED EIGHTEEN HOURS; BILE COLLECTED WITH ANIMAL FASTING. FASTED FIVE HOURS; FED VARIOUS FOOD-STUFFS TWO HOURS BEFORE BEGINNING COLLECTION OF BILE.

	Secretion, cc.			Bile pigment, mg.	Taurocholic acid, mgr.			Hemoglobin per cent.	Erythrocytes (millions).	Leukocytes (thousands).	Weight.	Procedure.
	First two hours.	Second two hours.	Third two hours.	Total.	Total.	Each six hours.	Total.					
1921.												
April 28.	9.7	6.7	8.3	24.7	17.3	..	351.6	70	5.63	27.0	7.5	Fasting.
May 30.	7.4	6.4	8.5	22.3	24.5	..	165.9	7.9	..
Average	6.9	7.3	6.8	21.0	23.1	..	165.9	7.7	..
3.	10.3	10.8	10.4	31.5	22.0	1.81	260.25	7.7	..
7.	12.7	10.9	8.0	31.6	23.7	..	236.3	7.9	..
Average	8.0	9.4	8.4	31.55	22.85	2.95	173.8	80	5.91	16.0	7.6	Lean meat, 160 gm.
10.	8.0	7.1	7.0	23.1	21.9	..	152.2	7.75	..
12.	8.0	7.1	7.0	23.1	21.9	..	152.2	7.9	..
Average	6.5	8.4	6.5	23.93	10.8	2.49	121.8	7.95	..
14.	6.5	8.4	6.5	21.4	15.5	..	258.9	80	6.17	11.1	7.6	Milk, 400 cc.
17.	7.1	8.8	9.0	24.9	18.7	..	215.3	7.5	..
19.	7.3	7.2	7.2	22.2	15.5	..	237.1	7.9	Lard, 35 gm.
Average	10.0	8.4	7.5	22.8	16.6	2.16	155.4	7.67	..
21.	10.0	8.4	5.8	23.6	18.9	..	210.7	84	6.88	12.8	7.9	Sugar, 70 gm.
24.	17.8	24.75	23.35	2.96	198.0	7.9	Water, 500 cc.
Average	20.85	20.85	2.67	204.45	7.9	..
General av.	25.13	20.85	Splenoctomy, May 25						
May 28.	10.7	9.6	9.3	29.6	39.9	100	7.08	10.05	7.5	Fasting.
31.	7.5	5.6	6.1	19.2	27.8	..	135.3	7.0	..
June 9.	8.1	6.3	5.8	20.2	19.2	..	202.6	7.4	..
16.	6.6	6.7	6.2	19.5	22.4	..	257.7	7.8	..
Average	10.0	8.7	10.2	22.1	27.35	3.68	198.5	7.425	..
7.	11.	8.7	9.6	28.0	15.9	..	116.5	85	5.80	15.6	7.9	Milk, 400 cc.
Average	12.2	10.1	9.6	31.9	19.9	..	377.6	8.2	..
2.	15.0	11.9	11.1	38.0	28.8	2.22	247.05	8.05	Lean meat, 160 gm.
4.	17.0	12.7	11.5	41.2	18.5	..	181.2	90	6.04	16.4	7.3	..
Average	10.0	9.4	8.1	39.6	23.65	3.2	181.2	7.4	..
14.	10.0	9.4	8.1	27.5	14.4	..	299.7	7.8	Lard, 35 gm.
18.	10.1	13.0	9.1	32.2	10.5	..	407.6	82	4.88	13.6	8.2	..
Average	21.	10.0	9.5	33.3	16.7	1.56	333.65	8.0	..
23.	13.8	9.8	8.0	28.5	16.7	..	302.3	8.5	Sugar, 70 gm.
Average	10.7	9.8	8.0	30.9	16.9	1.95	218.0	8.8	Water, 500 cc.
General av.	30.61	19.65	2.52	248.1	8.65	..

3 mg. for each kilogram of body weight for six hours (except in the case of Dog E168, when the value was about 5 mg.). These values are somewhat higher than those given by Whipple and Hooper (1 mg. for each pound for each six hours). Definite conclusions with regard to the normal variations in the amount of secretion of bile pigment on different diets do not seem warranted from these experiments. The variations were probably due to other factors, which will be discussed. This is especially evident in the graphs which seem to indicate that the amount of bile pigment secreted is largely independent of the food intake. A marked increase in the output of bile pigment after feeding carbohydrates, as reported by Hooper and Whipple, was not found.

After splenectomy, the average output of bile pigment remained practically unchanged, as shown in the three dogs that were splenectomized. However, the detailed findings, best shown in the graphs, are suggestive. In the two instances in which determinations were taken three days after splenectomy, a marked increase in output of bile pigment occurred the first few days after removal of the spleen. A possible explanation of this, of course, is that it may be due to the absorption of the hemoglobin liberated into the tissues by the operative procedure. To prove this it will be necessary as a control, to operate without removing the spleen. Yet in the instance of Dog E335 (Chart 2) the increased output of bile pigment was so marked that this factor seemed insufficient to explain the phenomenon completely; furthermore, the fact that the percentage of hemoglobin presented a similar and coincident increase is noteworthy.

After this preliminary increase, following operation and removal of the spleen, the output of bile pigment sank below normal, only to rise again. This reaction can be seen in all three charts, but is best studied in Chart 3, in which determinations are presented for almost three months after splenectomy. The decrease in output of pigment reached its lowest point in the different experiments from the tenth to the twenty-fifth day after splenectomy. After this period the curve representing pigment secretion swung above normal (Chart 3). However, it did not remain so, but a strange fluctuation continued, which was cyclic. It may be noted that the intervals between the points representing the greatest pigment output, and also between those representing the least output, correspond approximately to periods of one month; further minor variations of less extent seemed to occur between these more marked periods. A suggestion of this cyclic variation in output of bile pigment may also be seen in Chart 2, in which a normal cycle of about twenty-one days occurred before splenectomy. The fluctuations of pigment output were very much greater after splenectomy, and if there was a normal cyclic variation in secretion of bile pigment, this variation seemed markedly accentuated by removal of the spleen. This idea of the presence of cyclic variations in output of

TABLE IV.—DETERMINATIONS OF BILIARY SECRETION BEFORE AND AFTER SPLENECTOMY IN DOG E168. FASTED EIGHTEEN HOURS. BILE COLLECTED DURING FASTING; FASTED-FIVE HOURS, FED VARIOUS FOODS TWO HOURS BEFORE BEGINNING COLLECTION OF BILE. FASTED FIVE HOURS, FED VARIOUS FOODS TWO HOURS AFTER BEGINNING COLLECTION OF BILE.

	Secretion, cc.				Bile pigment, mg.				Taurocholic acid, mg.				Blood count.			Wt.	Procedure.
	First two hours.	Second two hours.	Third two hours.	Total.	First two hours.	Second two hours.	Third two hours.	Total.	First two hours.	Second two hours.	Third two hours.	Total.	Each six hours.	Hemoglobin, per cent.	Erythrocytes (millions).		
1921.																	
Mar. 5	5.3	7.2	8.1	20.6	11.3	15.4	17.8	44.50	164.0	100.8	101.2	366.0	..	82	6.62	11.40	8.50
7	7.2	6.7	6.5	20.4	14.9	17.7	14.6	47.20	50.6	60.9	16.2	127.7	8.30
Average	10.0	8.0	10.3	20.5	15.5	15.2	19.0	45.85	156.4	83.2	43.0	246.8	29.38	8.40
8	7.8	8.3	7.2	23.3	15.2	15.3	14.4	44.90	56.3	48.9	59.8	165.0	8.30
9	25.8	8.20
Average	9.8	8.6	8.4	26.8	15.2	12.5	11.9	39.60	64.6	47.7	63.3	223.8	27.13	8.25
10	8.6	9.0	9.7	27.3	15.0	14.5	16.5	46.10	69.7	81.3	49.0	200.0	7.80
11	8.6	9.0	9.7	27.3	15.0	14.5	16.5	46.10	69.7	81.3	49.0	200.0	7.70
Average	11.6	10.4	9.5	27.95	13.9	14.0	14.3	42.85	241.3	137.0	140.6	568.9	24.2	7.75
12	7.5	4.5	7.0	19.0	9.4	10.1	11.2	30.70	96.0	102.2	97.3	295.5	..	75	7.52	11.10	7.70
16	25.25	7.40
Average	5.0	8.0	9.8	22.8	10.0	13.2	14.2	36.45	99.0	101.6	100.9	301.5	57.25	7.55
17	6.8	10.8	9.6	27.2	11.7	15.1	14.9	41.70	119.0	126.3	227.3	472.6	7.70
18	25.0	39.55	387.0	49.9	7.80
Average	6.4	12.6	12.2	31.2	8.3	12.0	9.2	29.50	96.6	209.6	190.3	556.5	74.2	7.75
19	7.50
21	4.5	8.0	7.0	19.5	11.9	16.2	13.8	41.9	200.5	62.4	98.8	430.7	61.5	7.00
22	8.5	6.0	7.8	22.3	9.8	8.7	12.1	30.60	87.1	142.4	99.8	329.3	46.4	70	6.06	11.15	7.10
General av. (before splenectomy)	24.58	39.44	349.3	45.4	7.70

Splenectomy, March 23.

	Mar. 20	6.4	7.0	7.4	20.8	10.6	10.8	14.0	35.40	..	161.2	118.3	69.3	348.8	7.20
Fasting.	..	8.7	8.0	5.7	22.4	13.0	12.4	12.4	37.80	5.08	221.8	106.4	25.0	353.2	7.20
Milk, 400 cc, two hours before.	..	9.6	7.2	9.0	21.6	11.5	10.4	12.6	36.6	..	92.5	125.7	142.0	360.2	7.20
Lean meat, 160 gm., two hours before.	..	13.7	11.3	12.0	25.8	8.6	6.8	8.4	23.80	3.79	194.5	182.4	127.8	504.7	7.20
Lard, 35 gm., two hours before.	..	11.5	12.5	11.4	31.4	9.5	10.0	11.9	29.15	..	99.2	44.8	57.6	201.6	7.20
Sugar, 70 gm., and water, 500 cc, two hours before.	..	13.4	10.4	8.1	31.9	9.7	8.6	7.9	26.20	3.79	92.3	159.1	17.5	268.9	7.20
Lean meat, 160 gm., after two hours.	..	11.0	11.4	11.0	33.4	11.0	11.4	12.1	34.50	..	152.4	208.2	82.5	443.1	7.20
Lard, 35 gm., after two hours.	..	10.7	11.1	10.7	32.5	16.0	14.4	14.9	45.30	5.22	186.2	71.4	32.1	289.7	7.20
Sugar, 70 gm., and water, 500 cc, two hours before.	..	11.4	6.1	4.0	21.5	17.6	11.6	21.0	39.90	..	114.0	77.8	12.8	204.6	7.20
Lean meat, 160 gm., after two hours.	..	12.0	15.0	9.4	36.4	18.6	19.0	16.7	54.30	..	83.8	118.4	74.2	276.4	7.20
Lard, 35 gm., after two hours.	..	6.8	16.3	19.2	28.95	10.2	19.5	20.1	52.25	6.26	184.9	204.8	105.6	495.3	28.8	..	7.20
Sugar, 70 gm., and water, 500 cc, after two hours.	..	5.0	8.0	7.4	42.3	20.7	22.0	18.3	49.80	6.30	34.5	200.3	217.5	452.3	62.7	..	7.20
Fasting.	..	9.8	11.1	7.0	20.4	14.2	19.1	10.8	61.00	7.63	120.5	119.9	88.9	329.3	56.5	..	7.20
Lean meat, 160 gm., after two hours.	..	3.4	8.2	4.8	16.4	5.8	8.8	4.8	44.10	..	100.6	77.9	13.2	191.7	7.20
Lard, 35 gm., after two hours.	22.15	31.75	3.8	260.5	31.2	..	7.20
Sugar, 70 gm., and water, 500 cc, after two hours.	29.18	41.15	5.25	354.2	45.2	..	7.20
Fasting.	..	5.2	2.7	4.3	12.2	11.7	15.4	18.7	45.80	..	95.5	10.3	52.5	158.3	7.20
Lean meat, 160 gm., after two hours.	..	6.1	2.6	3.4	12.1	9.4	12.7	15.3	37.40	..	85.4	7.20
Lard, 35 gm., after two hours.	..	5.5	3.3	5.0	13.8	22.8	16.1	22.5	61.40	..	101.2	41.9	74.8	217.9	7.20
Sugar, 70 gm., and water, 500 cc, after two hours.	..	4.0	6.6	5.8	16.4	13.0	12.5	14.7	40.20	..	56.0	85.8	41.0	182.8	7.20
Lean meat, 160 gm., after two hours.	..	9.4	5.5	7.8	22.7	8.0	6.3	8.9	23.20	..	69.9	49.5	84.5	203.9	7.20
Lard, 35 gm., after two hours.	..	7.5	4.3	7.9	19.7	32.10	7.20
Sugar, 70 gm., and water, 500 cc, after two hours.	..	9.7	5.8	5.3	20.8	34.30	5.09	190.7	7.20
Fasting.	16.8	39.20	24.8	..	7.20

Chart 3. Dog 5160

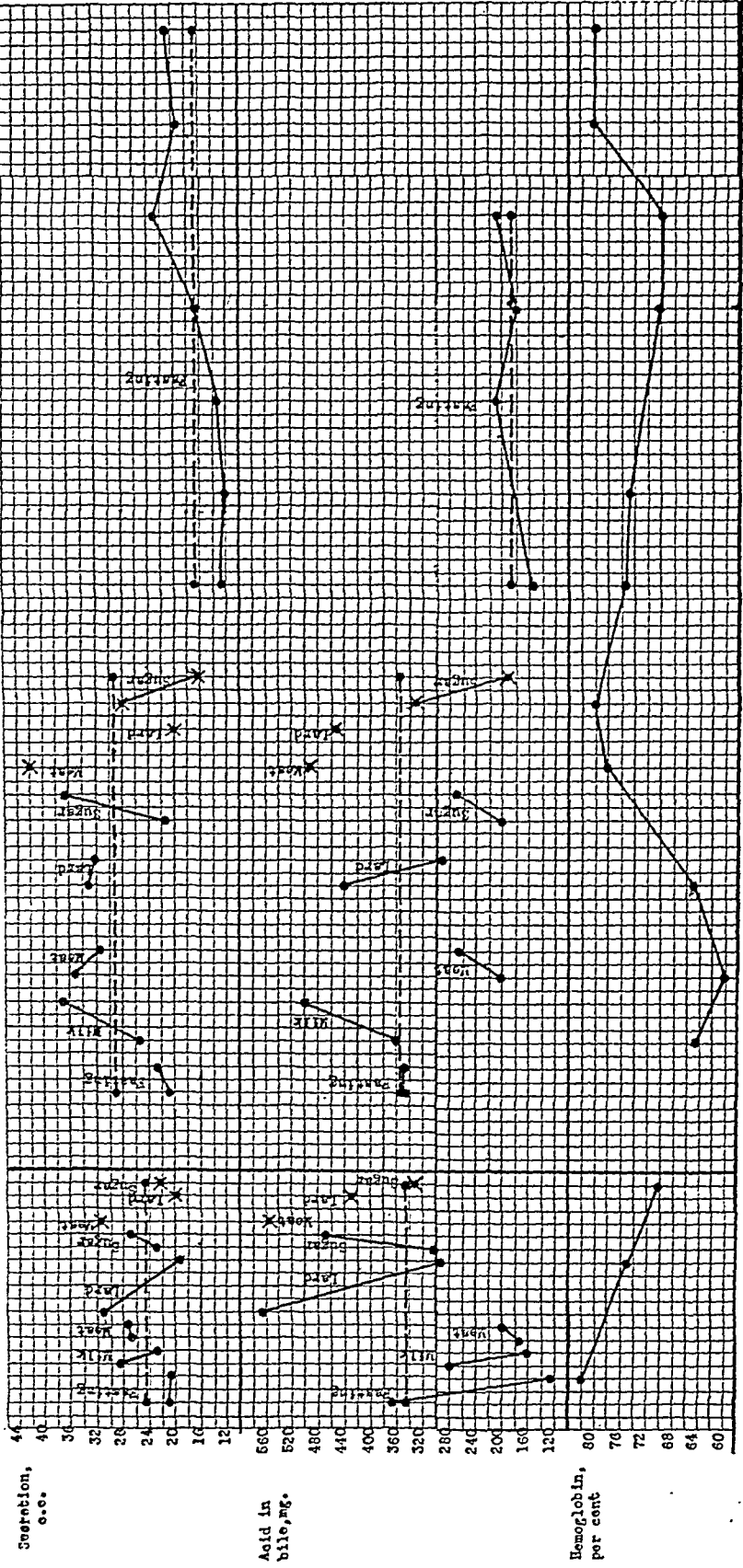


CHART 3

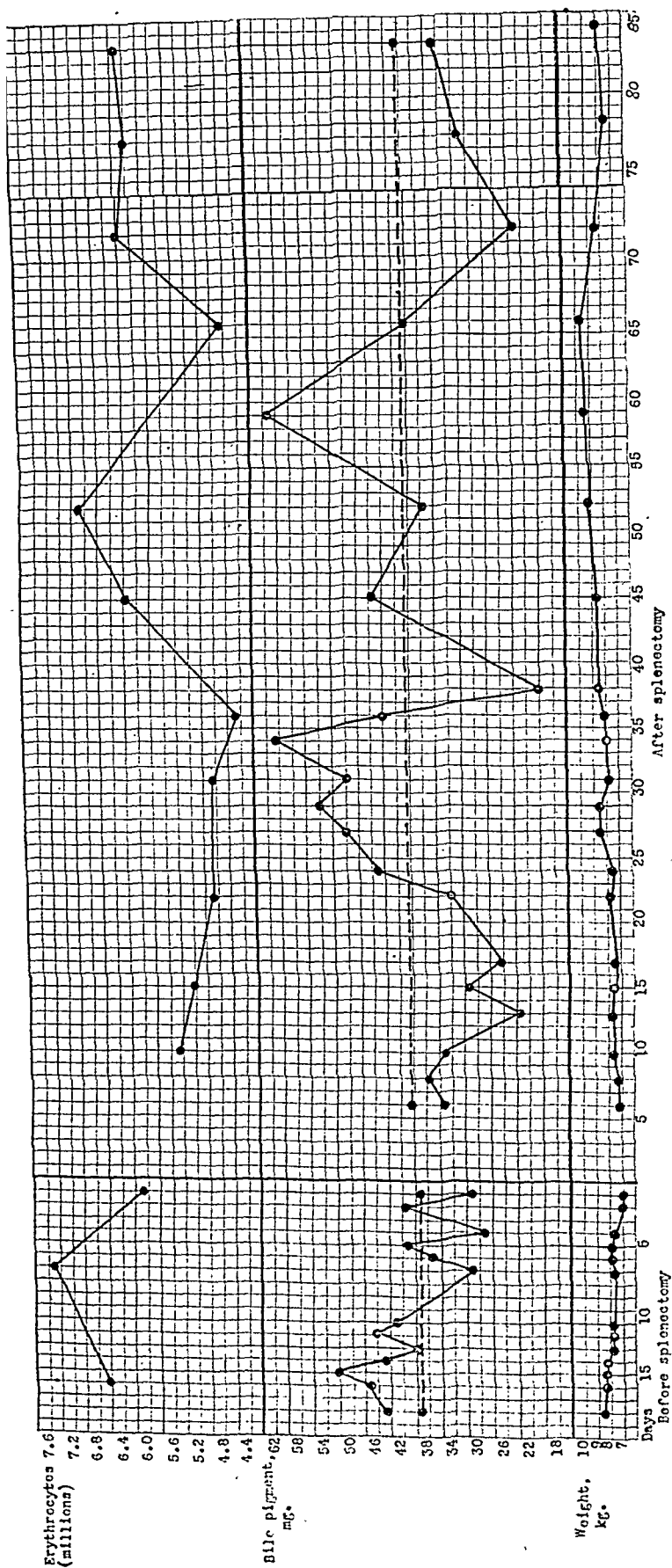


CHART 3 (Continued)

bile pigment finds support in the recently published observations of McMaster, Brown and Rous. They note wave-like variations in the normal output of bile pigment, and what appears to be a typical larger cycle is well shown in their text, Fig. 4, in which peaks of secretion of bilirubin are shown on the fifteenth and the forty-sixth days of the experiment, respectively. Likewise the findings of Ashby, that the destruction of the erythrocytes of transfused blood is not gradual and continual, but occurs by crises and in cycles, are quite suggestive in this connection.

The different types of food do not seem to play a part in the causation of these phenomena. It will be necessary to perform experiments over a long period, both in the normal animal, and after splenectomy, under conditions in which the food factor is not varied as it was in these experiments, and when more frequent and careful studies of the blood are carried out. Only then will definite conclusions be justified.

The parallelism between the amount of hemoglobin and the amount of bilirubin secreted is striking in all the graphs (the only place where this parallelism is not in evidence is in Chart 3 in which, after the first month following splenectomy, the marked fluctuations in the secretion of bile pigment are not present, or at least not present to the same degree, in the curve representing the percentage of hemoglobin). This is in harmony with the conception that these pigments may have a common origin; and indeed the findings of these experiments, as a whole, are difficult of explanation on the current theory that bile pigment is formed, at least to a considerable extent, by the transformation of hemoglobin liberated by destruction of erythrocytes in the spleen. Rather, the contentions of Whipple are supported by my investigation. The idea strongly suggests itself that the factor, or factors, responsible for the blood picture after splenectomy are responsible also for the change in the secretion of bile pigment after removal of the spleen.

The discordant results of the various investigators of the effect of splenectomy on the output of bile pigment may possibly be explained by the time period at which observations were made after splenectomy. Pugliese made the larger and more significant portion of his postsplenectomy determinations from nineteen to twenty-three days after removal of the spleen. In the experiments of Goto the normal postsplenectomy determinations were made from the sixth to the twelfth day, after which toluylendiamin was administered, and determinations continued until the eighteenth or nineteenth day. It will be noted that all these determinations have been made at times when the postsplenectomy output of bile pigment was at its lowest. The findings of Paulesco indicate merely the unit concentrations of bile pigment in the bile, and not the quantitative output of bilirubin. Since the concentration of pigment may vary greatly, and more or less inversely with the amount

of bile secreted, his results give no true indication of the output of pigment. The published data of Hooper and Whipple, which give the secretion of bile pigment in splenectomized dogs, begin more than four months after removal of the spleen. The present study is in agreement with their findings that the average output of bile pigment after splenectomy is unchanged.

Summary. The concept that the spleen influences the amount of bile pigment secreted by the liver has received common credence. The results of the experimental investigations of the effect of splenectomy on the output of bile pigment seem discordant. A diminution to one-half the normal values on removal of the spleen was found by Pugliese, Charrin and Moussu and Goto. Paulesco and Whipple and Hooper found no diminution in the secretion of bile pigment after splenectomy.

In the present study, experimental data regarding the biliary secretion in four dogs, three of which were splenectomized, are offered. The outstanding features of the normal secretion of bile in dogs with biliary fistulas are: The greatest flow of bile occurs during the feeding of meat, and the least during fasting. The amount of bile acid fluctuates greatly; it seems greatest on meals of lard and of meat; it is greater when the amount of bile secreted is greater, and less when the amount of bile secreted is less. The output of bile pigment from hour to hour is remarkably uniform. It does not vary with the amount of bile secreted; the concentration of pigment is low when the amount of bile is great, and high when the amount of bile is small; the total amount of pigment remains about constant. On the average, about 3 mg. of bilirubin are secreted for each kilogram of body weight in six hours. The output of pigment seems to be little influenced by the food taken.

The effects of splenectomy are: The amount of bile secreted when food is given is increased about one-fourth above the amount under similar conditions before splenectomy. Fluctuations in the amount of bile are more marked. The amount of bile acid remains about the same. There is an immediate slight rise in the percentage of hemoglobin of the peripheral blood and in the erythrocyte count, which is followed by anemia in which the percentage of hemoglobin falls more rapidly and tends to return toward the normal more rapidly than does the erythrocyte count. The curve representing the output of bilirubin resembles that representing the percentage of hemoglobin. There is an immediate rise after splenectomy, followed by a fall to much below normal which is most marked between the tenth and twenty-fifth days. The curve then rises again. The fluctuations in output of bile pigment are much more marked. The average amount of pigment secreted, when totalled over a sufficiently long period, remains the same. It is suggested that the discordant results of previous investigators may be merely an expression of the above reaction, and due to the varying length of time after splenectomy at which determinations were made.

It is probable that there is a normal cyclic variation in the output of bile pigment. The chief fluctuations seem to come at intervals of approximately one month; between these are minor fluctuations. These fluctuations are markedly accentuated by removal of the spleen.

The hypothesis is proposed that the factor or factors responsible for the blood picture after splenectomy are responsible also for the reaction in the secretion of bile pigment after removal of the spleen; and if there is a cyclic mechanism in the elaboration of bile pigment, that the spleen in some manner exercises a regulatory influence in this phenomenon.

BIBLIOGRAPHY.

1. Ashby, Winifred: Study of Transfused Blood (I. The Periodicity in Eliminative Activity Shown by the Organism), *Jour. Exper. Med.*, 1921, 34, 127.
2. Ashby, Winifred: Study of Transfused Blood (II. Blood Destruction in Pernicious Anemia), *Jour. Exper. Med.*, 1921, 34, 147.
3. Charrin and Moussu: Physiologie de la rate (fonction biligénique), *Compt. rend. Acad. d. sci.*, 1905, 140, 1118.
4. Cuvier: Quoted by Gray.
5. Foster, M. G., and Hooper, C. W.: Metabolism of Bile Acids (I. A Quantitative Method for Analysis of Bile Acids in Dog's Bile), *Jour. Biol. Chem.*, 1919, 38, 355.
6. Goto, K.: The Relation of the Spleen to Blood Destruction and Regeneration and to Hemolytic Jaundice (XVI. The Influence of Splenectomy and of Blood Disintegration upon the Production of Bile Pigment), *Jour. Exper. Med.*, 1917, 26, 795.
7. Gray, H.: On the Structure and Use of the Spleen, London, J. W. Parker, 1854, 380 pp.
8. Hooper, C. W., and Whipple, C. H.: Bile-pigment Metabolism (I. Bile-pigment Output and Diet Studies, *Am. Jour. Physiol.*, 1916, 40, 332.
9. Hooper, C. W., and Whipple, C. H.: VIII. Bile-pigment Output Influenced by Hemoglobin Injection, Splenectomy and Anemia, *Am. Jour. Physiol.*, 1917, 43, 275.
10. Inlow, W. DeP.: The Spleen and Digestion (I. The Spleen and Gastric Secretion), *AM. JOUR. MED. SCI.*, 1921, 162, 325.
11. Inlow, W. DeP.: The Spleen and Digestion (II. The Spleen and Pancreatic Secretion), *AM. JOUR. MED. SCI.*, 1922, 164, 29.
12. Inlow, W. DeP.: The Spleen and Digestion (III. The Spleen in Inanition: The Effect of the Removal of the External Secretion of the Pancreas of the Spleen), *AM. JOUR. MED. SCI.*, 1922, 164, 173.
13. Lieutaud, J.: Essais anatomiques, contenant l'histoire exacte de toutes les parties qui composent le corps de l'homme, Paris, Huart, 1742, 308 (quoted by Gray).
14. Lieutaud, J.: Observation sur la grosseur naturelle de la rate, *Mém. de l'acad. de Paris*, 1738 (quoted by Gray).
15. McMaster, P. D., Brown, G. O., and Rous, P.: Studies on the Total Bile (I. The Effects of Operation, Exercise, Hot Weather, Relief of Obstruction, Intercurrent Disease and Other Normal and Pathological Influences), *Jour. Exper. Med.*, 1923, 37, 395.
16. Mann, F. C.: A Technic for Making a Biliary Fistula, *Jour. Lab. and Clin. Med.*, 1921, 7, 84.
17. Paulesco, N. C.: La splenectomie ne modifie pas la sécrétion biliaire, *Jour. de physiol. et de path. gén.*, 1906, 8, 22.
18. Pearce, Krumbhaar and Frazier: The Spleen and Anemia, Philadelphia, Lippincott, 1918, 419 pp.
19. Ponfick, E.: Ueber Hämoglobi-nämie und ihre Folgen, *Berl. klin. Wchnschr.*, 1883, 20, 389.
20. Pugliese, A.: La secrezione e la composizione della bile negli animali smilzati, *Policlinico*, 1899, 6, sez. med., 121.

21. Pugliese, A.: Neuer Beitrag zur Physiologie der Milz, das Eisen der Galle und des Blutes bei entmilzten Tieren, *Biochem. Ztschr.*, 1913, 52, 423.
22. Pugliese, A., and Luzzatti, T.: Contributo alla fisiologia della milza, *Arch. per le sci. med.*, 1900, 24, 1.
23. Whipple, G. H., and Hooper, C. W.: Bile-pigment Metabolism (III. Bile-pigment Output and Blood Feeding), *Am. Jour. Physiol.*, 1917, 42, 256.
24. Whipple, G. H., and Hooper, C. W.: Bile-pigment Metabolism (VI. Bile-pigment Output Influenced by the Eck Fistula), *Am. Jour. Physiol.*, 1917, 42, 544.
25. Wisner, F. P., and Whipple, G. H.: Variations in Output of Bile Salts and Pigments During Twenty-four-hour Periods; Observations on Standard Bile-fistula Dogs, *Am. Jour. Physiol.*, 1922, 60, 119.

BLOOD COUNTS AND BASAL METABOLISM OF LEUKEMIAS UNDER ROENTGEN-RAY TREATMENT.*

BY KENNETH R. McALPIN, M.D.,

AND

BERTRAM J. SANGER, M.D.,

NEW YORK.

(From the Department of Medicine of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York.)

THE literature on the treatment of leukemias is so extensive that one feels not a little hesitation in attempting to add anything to so carefully covered a field. The effect of roentgen-ray treatment on the 16 cases here reported is thought to be of interest as the results are considered from three different viewpoints.

1. Effect on blood count.
2. Effect on basal metabolism.
3. Effect on weight and general well-being.

Former observers frequently pointed with pride to a dramatic drop in the blood count when a case of leukemia was treated with roentgen-ray or radium. It is also admitted that some cases show a drop in basal metabolism and few will deny that most patients gain weight when so treated, but most observers agree that the prognosis is always hopeless, and aside from a temporary improvement, radiotherapy does nothing: Peabody,¹ Ordway,² Levin,³ Renon and Degrais,⁴ Oppenheimer,⁵ Stern,⁶ Gulland,⁷ Vogel,⁸ Henriques and Menville,⁹ Klewitz and Schuster,¹⁰ Bécélère and Bécélère¹¹ and Pancoast.¹²

It is unwise to try to refute such a wealth of evidence, but is

* Read before the Section on Medicine at the Academy of Medicine, May 15, 1923.

FOREWORD.—The radiotherapy referred to in this article was first directed by Dr. James Corscaden, then by Dr. W. D. Witherbee and finally by Dr. Ross Golden, to all of whom the writers are very much indebted and wish to acknowledge appreciation of their help, without which it would have been impossible to treat these patients.

it not worth while to at least attempt to find definitely how much treatment these patients should have and to learn if there is any indication for beginning treatment after a prolonged remission? Too much importance has perhaps been devoted to reducing the blood count and too little time has been spent in studying the blood picture of the patient while the count is low.

No attempt was made to study the chemical metabolism, as this work has already been done. Most observers believe that there is a marked increase in the uric acid output in the urine: Magnus-Levy,¹³ Edsall,¹⁴ Musser and Edsall,¹⁵ and Knudsen and Erdos.¹⁶ Folin and Denis¹⁷ found a distinct elevation in blood uric acid.

In chronic leukemia there is some variation in the nitrogen balance, but for the most part this is negligible in either direction. Certainly there has been no change noted that is commensurate with the great rise in total metabolism as manifest by the increased heat production: Von Noorden,¹⁸ Magnus-Levy,¹³ Taylor,¹⁹ Musser and Edsall,¹⁵ Goodall,²⁰ Stejskal and Erben,²¹ Döri²² and others.

Murphy, Means and Aub²³ made some careful calorimetric studies on a case following roentgen-ray and radium treatment.

In the present series it is evident that treated cases show a fall in total white cell count, and a similar fall in basal metabolism. This drop in basal metabolism does not usually occur in normal individuals as it has not been observed in a few cases of carcinoma after massive doses of roentgen ray. These cases do not show any appreciable change in their basal metabolism.

The most brilliant as well as the most lasting effects were usually obtained in the myeloid cases, notwithstanding the fact that theoretically one would expect the lymphocyte to be the more readily affected.

The basal metabolism not only fell with the white blood cells, but seemed to parallel the curve. If the blood count went up after reaching normal limits the basal metabolism would also rise. And occasionally the metabolism preceded the rise in the white cells. Owing to the difficulty of doing a basal metabolism at exactly the right time it is hard to illustrate this fact, which may well be of more frequent occurrence. This metabolic rise is of real value from the standpoint of prognosis and treatment.

This paper is based on 16 cases of leukemia that have been studied during the last four and a half years at the Presbyterian Hospital. The patients have all been admitted to the wards and have been followed up as carefully as possible after their discharge. It is always difficult to keep in touch with patients over long periods of time and those dealt with have proved to be no exception to the rule. Several have died in other institutions or in their own homes. This is regrettable but unavoidable. Only 1 of 6 still living has been lost track of. This is a young Irish woman who did splendidly under treatment and felt so well that a year ago she

braved a trip to her native land. Since then all attempts to locate her have failed. Patients do not relish a trip to the hospital without breakfast and basal metabolism determinations have suffered in consequence.

In the following plates the radiotherapy is indicated by a line. The length of these lines indicate the amount of the treatment. The longest line, four divisions, represents a full dose, that is just under an erythema dose.

The number of lines in each division indicate the frequency of the treatments. So by glancing at the chart a very fair idea is given not only of the frequency of the treatment, but also of the amount given at each time.

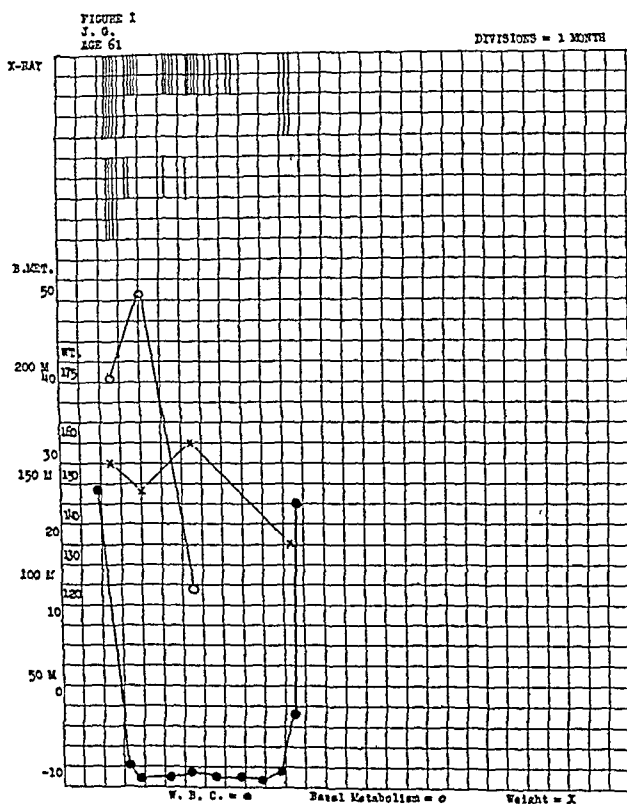
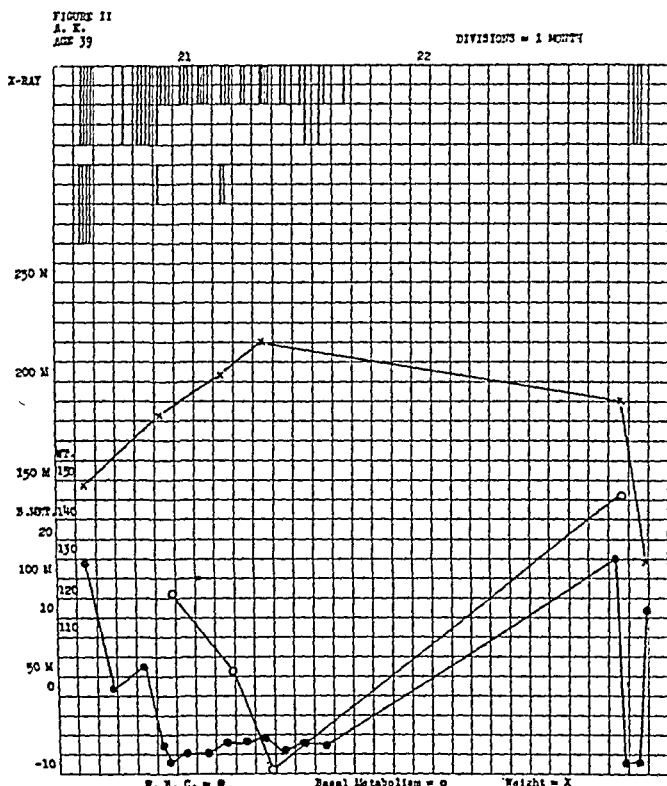


FIG. 1 represents the treatment and course of patient 2. He was a rather ignorant, old man who had had a cerebral hemorrhage and suffered acutely from emphysema. His white cells dropped rapidly as indicated; his basal metabolism, after a temporary rise, dropped to normal limits and for a time he gained weight. The chart illustrates very nicely that when his count and basal metabolism were low, his weight was high; at this time he was in his best condition. Later he had an operation for mastoid and came in the hospital with a rapidly rising blood count. His emphysema was severe, but strangely enough death apparently was due to a cerebral hemorrhage. No postmortem was obtained. The fact that no basal metabolism was done over the last of the course was due directly to his cough.

To avoid too long a discussion it is perhaps wise not to go into the details of the differential counts. These counts, however, have been done and the actual number of the various cells have been calculated. One fact seems obvious, when the treatment is satisfactory the pathological cells decrease, that is the myelocytes

go down in myeloid and lymphocytes in the lymphoid type. This decrease is, of course, actual.

It might be of interest to mention that one case of myeloid leukemia lost all signs and symptoms of the disease for about six months. The spleen and glands were not palpable; the total white count varied from 10,000 to as low as 1300 and the myelocytes disappeared from the circulating blood. Later the count went up to 160,000 white cells and the spleen reappeared, showing that the aleukemic phase spoken of by Ordway and Gorham²⁴ can be brought about by radiotherapy.



spark gap, 8 inches. Filter: wood, 1 cm.; leather, 4 mm.; aluminum, 1 mm.; Bakelite, 2 mm.

Fifty milliamperes minutes was just under an erythematous dose, and this is what the patients were usually given at first. The next modification was changing the filter to 3 mm. of aluminum alone, and finally, when a more modern machine (Waite and Bartlett) was installed the spark gap was increased to 9 inches and the dose was cut down to 35 ma. minutes.

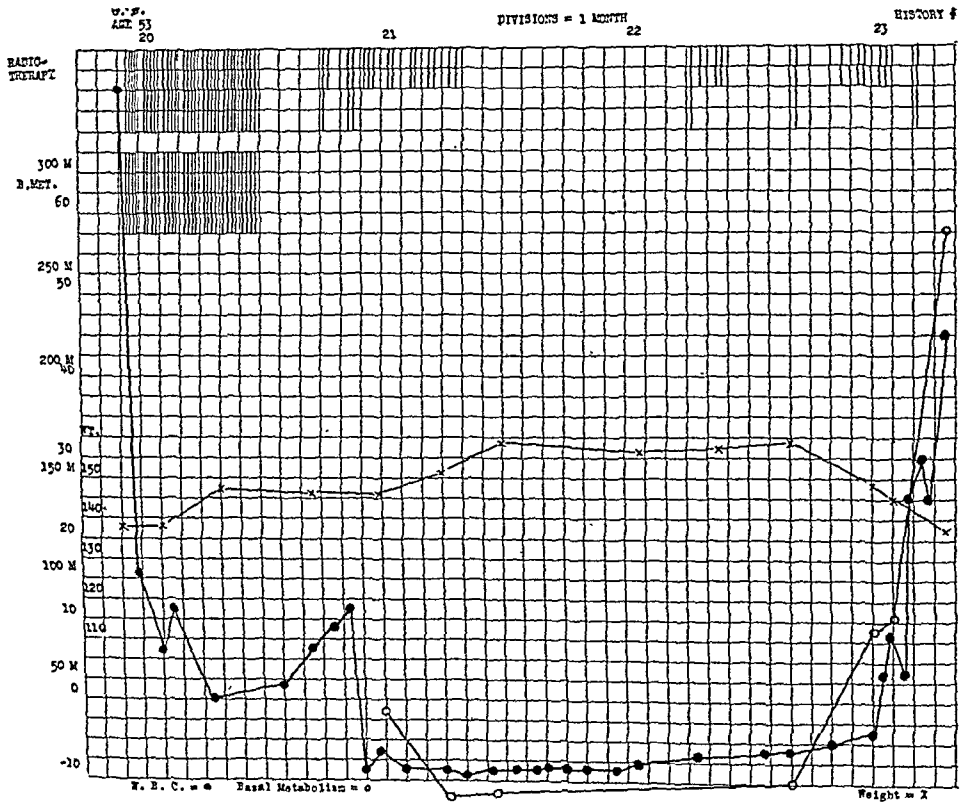


FIG. 3 is that of a man, aged fifty-three years, who had myeloid leukemia. When he was first observed basal metabolism was not being done, and so most unfortunately we have no early observations. The chart is interesting, as at the last after three years of treatment it shows the rise in basal metabolism and white cells with a corresponding drop in weight. This man died at home, the typical picture of myeloid leukemia for whom nothing could be done. Although this man died he had at least two years with no symptoms after the disease was well established.

The trunk was divided into 6 areas anterior and 6 posterior. One treatment usually covered 3 of these areas or approximately half of the chest and abdomen. Rarely, a similar region was treated on the opposite side of the body at the same sitting.

In a few cases the spleen alone was treated and sometimes the long bones. When necessary the exposure was made to cover the neck or axillæ.

Treatments were at first given once or twice a week, depending on the way the patient reacted and the effect on the blood count. As a rule it was thought best to reduce the treatment when the

count continued to go down. This seems reasonable, as there is no doubt but that the effect is cumulative. There is no definite rule as to how low the count should be; it is probably wise to stop treatment for a week when 50,000 is reached, after a steady fall from the neighborhood of 200,000. From 50,000 one should proceed with caution and *always* take a white count *before* treating. As 20,000 is approached the patient should be watched with increasing care and a further reduction is questionable. It may be said

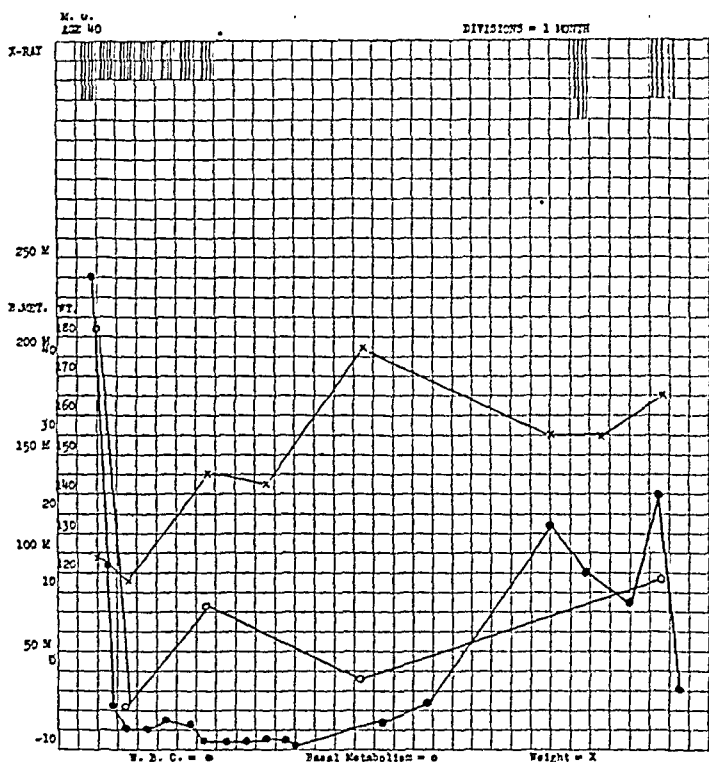


FIG. 4.—This is the woman referred to above, who had myeloid leukemia and became anemic under treatment. The chart illustrates rather well the fall in basal metabolism with a corresponding drop in white blood cells with a very definite increase in weight. A later rise in blood count had a corresponding rise in basal metabolism. She responded to treatment well and when last seen was doing fairly well. Another point which she illustrates is that she felt quite well with no idea that she was having a recurrence, until, as indicated, her white cells had risen to over 100,000 and her spleen became enlarged.

that, judging from the present series, patients do well with a count of 10,000 or even lower, but such a count must be reached only after several months of treatment. The length of each treatment should be reduced and the time between sittings extended. It is sometimes wise to treat only once every month or six weeks. In this way the patient may be kept in good condition and free from a recurrence; for how long, it is unwise to guess.

During a long course of treatment the red cells should not be

overlooked. In one case (M. G.) the red cells once reached the alarmingly low figure of 1,000,000 with a hemoglobin of 20 per cent. Although this did not immediately follow radiotherapy it was undoubtedly due to a delayed or accumulative effect of the treatment. This was the same individual who lost all signs of the disease. She improved after transfusions and her red cells went up to 3,100,000 with 69 per cent hemoglobin. She was feeling perfectly well and able to do her work when last seen, almost two years after her severe anemia.

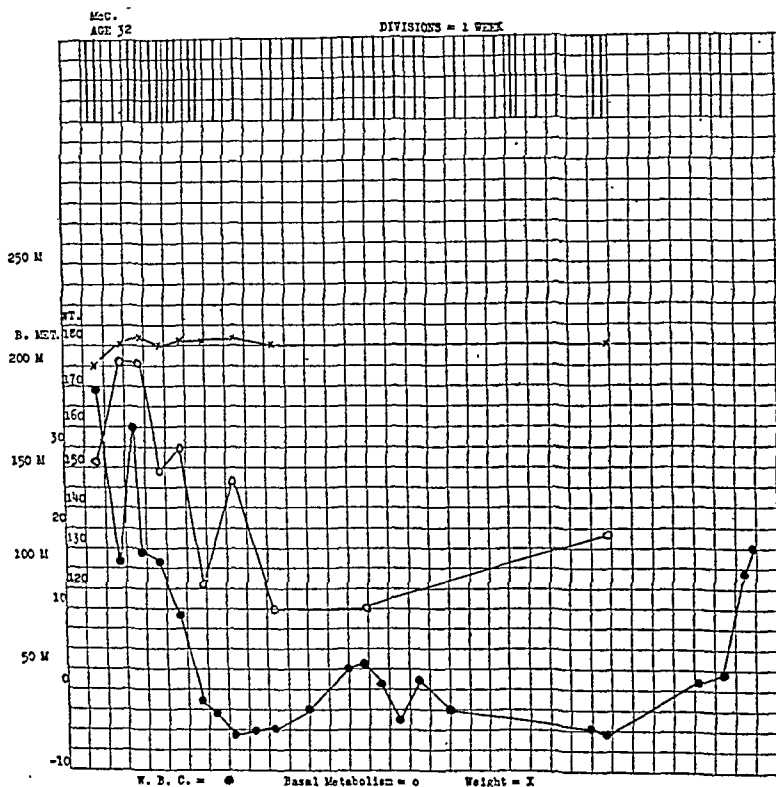


FIG. 5 is another myeloid leukemia who was very carefully followed for a short time. The divisions in the chart represent one week. The chart is interesting chiefly because of the detail and the fact that the basal metabolism had begun to rise when the white cell count continued low. This patient died soon after the last count was made.

"A. K." was another who may have been injured by the rays. He was a young man who had lymphoid leukemia. The glands of his neck and axillæ, which were tremendous, practically disappeared under treatment. His white cells fell from over 100,000 to under 10,000. He seemed perfectly well, and did not return for over a year. When he did appear his glands had become enlarged and his white cells had mounted to 112,000. He was given three treatments over large areas in ten days, and his count came down to 6000. Two weeks after treatment he came to the hospital bleeding from the gums and showing a purpuric eruption

on the lower extremities. Platelets were only 10,000, or too low to count accurately. He was transfused four times in six days, receiving 400, 500, 700 and finally 1000 cc of blood. The first was citrated. All of the others were whole blood. He died eight days after admission, or twenty-two days after the last treatment.

In some respects this case is similar to one reported by Dr. Witcher.²⁷ Dr. Witcher's case was a myeloid type and seemed to become aplastic, whereas the last counts in the present case showed a very great rise in white blood cells, up to 57,000, and finally 83,000. The last count was made three days before death.

One must feel that the treatment may have done harm, but, on the other hand, the final rise in white blood cells showed beyond any question that the process was still active and the outlook hopeless. Possibly the patient might have been helped had he returned earlier for treatment. Again, one can only speculate.

Detailed case histories take much valuable time and often prove of little value, so it has been decided to omit them. In their place will be shown charts, which illustrate the effect of the radiotherapy. In passing it may be said that the facts illustrated by these five examples are by no means unique, but because of more frequent observations and better facilities for study they are more complete.

Conclusions. 1. Roentgen-rays will not cure leukemia, but both of the chronic forms, especially the myeloid, respond to this form of treatment, and life may be made more comfortable as well as prolonged.

2. Patients should be watched indefinitely, even when they appear normal. A slight rise in blood count or basal metabolism may indicate a recurrence.

3. Blood counts are absolutely necessary as a check on the treatment. Patients may well be overtreated.

4. Basal metabolism is also a prognostic aid.

5. The patient is not always aware of an impending relapse.

CLASSIFICATION.

	Number of cases.	Living.	Dead.
Myeloid	8	4 (?)	4
Lymphoid	7	2	5
Mixed	1	0	1
Total	16	6 (?)	10

MYELOID.

Living.			Dead.		
Identification number.	Age.	Time observed.	Identification number.	Age.	Time observed.
15	23	6 mos.	5	38	8 mos.
12	34 (?)	5 mos.	10	43	1 yr., 1 mo.
1	42	2 yrs., 6 mos.	6	56	3 yrs., 6 mos.
8	53	3 yrs., 2 mos.	7	60	4 yrs., 10 mos.
Average 38 yrs.			Average 49 yrs.		

LYMPHOID.

Living.			Dead.		
Identification number.	Age.	Time observed.	Identification number.	Age.	Time observed.
4	39	2 yrs. 3 mos.	3	40	2 yrs., 6 mos.
14	66	1 yr.	2	62	1 yr.,
			9	64	1 yr., 5 mos.
			11	68	3 yrs.,
Average 52½ yrs.			Average 58½ yrs.		

MIXED.

Living.			Dead.		
Identification number.	Age.	Time observed.	Identification number.	Age.	Time observed.
0	0	0	13	66	3 mos.

Average time that each patient was observed—1 yr. 9 mos.

REFERENCES.

1. Peabody, F. W.: Report on the Treatment of Myelogenous Leukemia with Radium, *Boston Med. and Surg. Jour.*, 1917, 117, 873.
2. Ordway, T.: Remission in Leukemia Produced by Radium in Cases Completely Resistant to Roentgen-ray and Benzol Treatment, *Trans. Assn. Am. Phys.*, 1916, 31, 177.
3. Levin, I.: Roentgen-ray and Radium Treatment of Leukemia and Hodgkin's Disease, *Med. and Surg.*, 1917, 1, 411.
4. Renon, L., and Degrais, P.: Résultats éloignés de la curiethérapie de la leucémie myeloïde; valeur de la méthode et conduite de la cure, *Bull. de l'Acad. de méd.*, 1921, 85, 207.
5. Oppenheimer, W.: Beiträge zur Röntgenbehandlung der Leukämie, *Berl. klin. Wchnschr.*, 1921, 58, 1351.
6. Stern, L. D.: Radiation in Treatment of Blood Disease, *Jour. Michigan Med. Soc.*, 1922, 21, 324.
7. Gulland, G. L.: Discussion on Radiation in the Treatment of Disease of the Blood, *Brit. Med. Jour.*, 1921, 2, 271.
8. Vogel, K. M.: The Leukemias, *Nelson Loose-Leaf Living Medicine*, 4, 66.
9. Henriques, A., and Menville, L. J.: Radium in Myelogenous Leukemia, *New Orleans Med. and Surg. Jour.*, 1922, 75, 247.
10. Klewitz, F., and Schuster, E.: Zur Prognose der Leukämie, *Deutsch. med. Wchnschr.*, 1922, 48, 1003.
11. Bécélère, A., and Bécélère, H.: La radiothérapie dans les leucémies, *Trans. Internat. Cong. Med.*, London, 1913-1914, Section XXII, Part 2, p. 1.
12. Pancoast, H. K.: Leukemia, *Am. Jour. Roentgenol.*, 1917, 4, 611.
13. Magnus-Levy, A. von: Ueber den Stoffwechsel bei acuter und chronischer Leukämie, *Virchow's Arch. f. path. Anat. u. Physiol. u. f. klin. Med.*, 1898, 152, 107.
14. Edsall, D. L.: A Case of Acute Leukemia with Some Striking Clinical Features; Observations on Metabolism in this Case and in a Case of Severe Purpura Hemorrhagica, *Trans. Assn. Am. Phys.*, 1905, 20, 279.
15. Musser, J. H., and Edsall, D. L.: A Study of Metabolism in Leukemia under the Influence of the Roentgen-ray: with a Consideration of the Manner of action of the Roentgen-ray and of Some Precautions Desirable in its Therapeutic Use, *Univ. Pennsylvania Med. Bull.*, 1905-1906, 18, 174.
16. Knudsen, A., and Erdos, T.: A Metabolism Study of a Case of Leukemia during Radium Treatment, *Boston Med. and Surg. Jour.*, 1917, 176, 503.
17. Folin, O., and Denis, W.: Protein Metabolism from the Standpoint of Blood and Tissue Analysis (Sixth Paper on Uric Acid, Urea and Total Non-protein Nitrogen in Human Blood), *Jour. Biol. Chem.*, 1913, 14, 29.
18. Van Noorden: *Lehrbuch der Pathologie des Stoffwechsels*, Berlin, 1893, p. 349.
19. Taylor, A. E.: Studies in Leukemia, Contributions from the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania, 1900, p. 148.

20. Goodall, H. W.: Nitrogenous Metabolism in a Case of Chronic Myelogenous Leukemia, *Boston Med. and Surg. Jour.*, 1914, **170**, 789.
21. Stejskal, C., and Erben, F.: Stoffwechselversuch bei lymphatischer und liemal-myelogener Leukämie, *Ztschr. f. klin. Med.*, 1900, **39**, 151.
22. Döri, Bela: Stoffwechseluntersuchungen bei einer mit Benzol behandelten chronischen leukämischen Myelose, *Wien. klin. Wchnschr.*, 1913, **26**, 2034.
23. Murphy, J. B., Means, J. H., and Aub, J. C.: Clinical Calorimetry (twenty-third paper): The Effect of Roentgen-ray and Radium Therapy on the Metabolism of a Patient with Lymphatic Leukemia, *Arch. Int. Med.*, 1917, **19**, 890.
24. Ordway, T., and Gorham, L. W.: Leukemia, *Oxford Med.*, vol. 2, 681.
25. Elliot, C. A.: Radium Treatment of Leukemia: One Case with Splenectomy, *Med. Clin. of North America*, 1918, **1**, 1261.
26. Vaquez, H., and Yacoël, J.: Un cas de leucémie myeloïde traitée depuis sept ans par le benzol et hématologiquement guérie, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1922, **46**, 1168.
27. Whitcher, B. R.: Blood Changes in Myelogenous Leukemia Following Radium Treatment, *Proc. New York Path. Soc.*, 1922, **22**, 44.

ROENTGEN-RAY THERAPY IN THE TREATMENT OF EXOPHTHALMIC GOITER.

BY G. M. GOODWIN, M.D.,

AND

W. B. LONG, M.D.,

NEW YORK.

(From the Medical and Radiotherapeutic Departments of St. Luke's Hospital,
New York.)

THERE is much difference of opinion as to the exact etiology and the proper method of treatment of exophthalmic goiter. Some insist that surgery is the only effectual method of treatment; others, impressed by the surgical risk and the frequency with which recurrence of the symptoms is seen after operation, go to the other extreme of condemning surgery altogether. Of recent years some observers have reported enthusiastically on the results of roentgen-ray therapy. The readiness with which the patients submit to it and the absence of risk recommend it. This report is submitted, not particularly to recommend roentgen-ray therapy, but to record our observations on the clinical course of cases of hyperthyroidism so treated. We believe also that the record of a series of similar observations made on a number of cases over a period of months may be of some value as a contribution to the study of thyroid disorders.

The cases selected for this study have been of the toxic exophthalmic type. They presented general enlargement of both thyroid lobes and isthmus, the swelling being diffuse and smooth, not nodular. No cases of toxic adenoma are included in this group, since there seems to be little doubt that surgery is the proper

method of treatment in this type. In addition to the thyroid tumor these cases presented the usual symptoms of thyroid toxemia, such as tachycardia, sweating, exophthalmos, loss of weight, and increased metabolism.

On admission to the clinic the patients were advised as to a general routine. They were directed to save themselves as much as possible, to rest for two hours every afternoon, to retire regularly at 9.30 P.M., after a long warm bath, and to take extra nourishment in the form of milk drinks between meals. In some cases where the home duties were particularly strenuous they were admitted to the hospital or sent to convalescent homes for two or three weeks. From the standpoint of the purely scientific investigation of the effects of roentgen-ray therapy, the introduction of other factors, such as additional rest, is perhaps faulty technic, but the patient's good was always our primary consideration. At all events, the social condition of these patients was no better than that of the average clinic patient (mothers, housewives and domestics), and this general advice was so poorly followed that we think it may be fairly said that it had small influence on their progress.

While under observation the patients were instructed to return to the clinic each week. Here, on each visit, a record was made of their weight, pulse-rate, and subjective symptoms. The severity of the latter was recorded as +, ++, +++, and +++++. There is, of course, no accurate way of measuring such symptoms, but this method serves fairly well as a record of one's impression of them. Estimations of the basal metabolic rate were made at frequent intervals. They were also instructed to report each week for treatment at the Radio-therapeutic Department.

The roentgen-ray technic employed consisted in the administration of approximately two-fifths of an erythema dose, filtered through aluminum, to alternate sides of the neck each week. The region to which the application is made embraces that part of the neck and thorax lying between the upper level of the thyroid and the upper level of the third rib. This permits the ray to reach the thyroid and also the thymus, if one be present. The patient lies on her back with the head turned to the right or left, as the case may be. A uniform distance of 35 cm. from the target to the skin is used. Filtration is accomplished by 3 mm. of aluminum. The potential at the tube terminals was 140,000 volts, peak, corresponding to a spark gap of 10 inches between points. Five milliamperes are used, and the time of exposure is uniformly five minutes, with the exception that in highly toxic cases this dose is still further reduced, for we have seen cases where even such a small dose seemed definitely to increase the toxic condition of the patient. Such a dose as this may be given weekly to alternate sides of the neck for months, and to all practical purposes without fear of permanent damage to the skin. It is only after six or eight such

treatments that the faintest tanning begins. Of course it is possible that in some cases we may eventually get some atrophy with telangiectasia, but in an experience of over five years we have not seen it.

We include below the summaries of 9 cases and the charts of 5 of these. The charts are copied from those used in the routine observation of patients in the thyroid clinic. On admission to the clinic a skeleton blank is supplied for each patient, containing

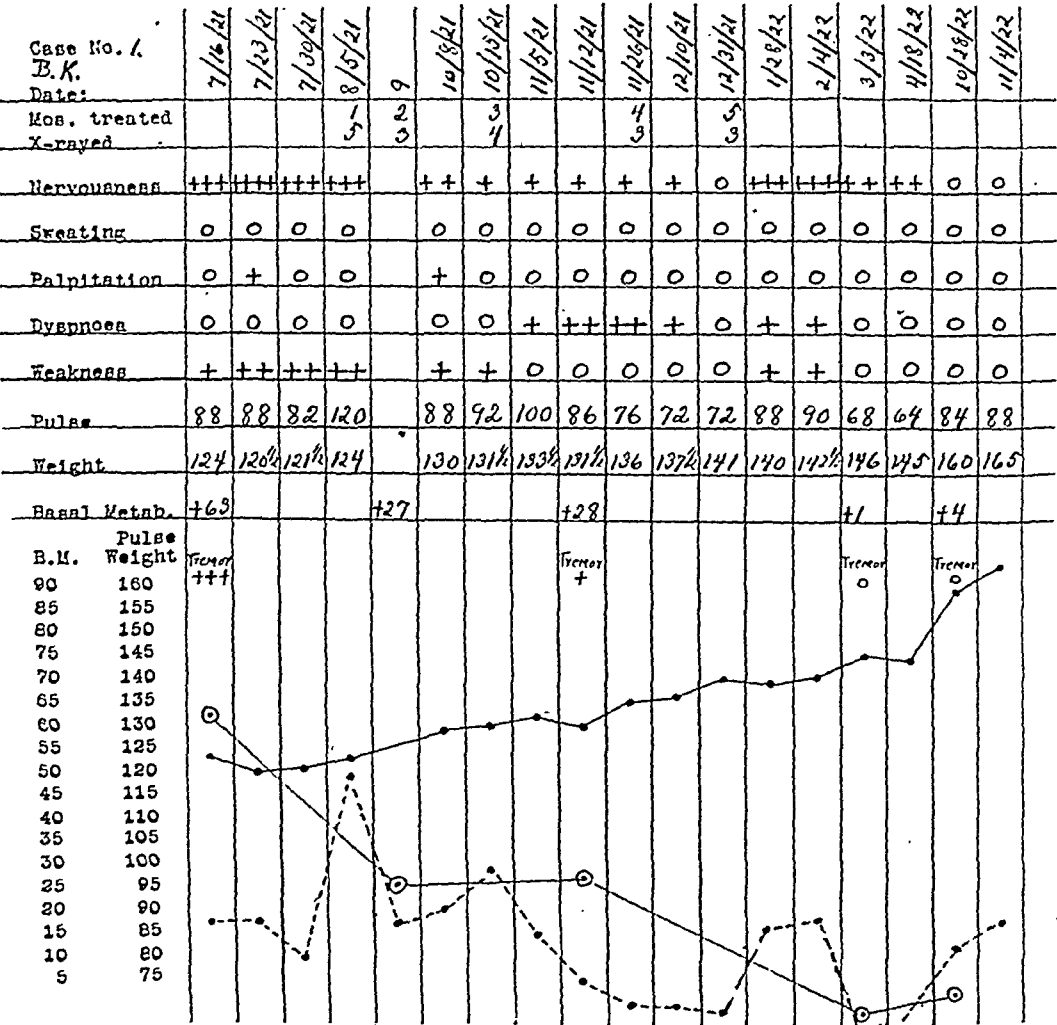


CHART 1

uniform data to be noted on each visit. On the lower part of this skeleton is a scale on which the pulse, weight and metabolism curves are graphed.

In these charts the pulse is represented by the broken lines; the weight by the continuous lines connecting dots, and the metabolism by continuous lines connecting small circles. On the top of the chart the date of the visit is noted; just below this the number

of months under treatment, and the number of roentgen-ray treatments in each month are given.

Examination of the summaries or charts of the first five of these cases, it would seem to us, gives the impression of very gratifying improvement under this type of therapy. The most striking thing is the gain in weight. One of these cases has gained 42 pounds; one 27 pounds, and all of them have gained 15 pounds or more.

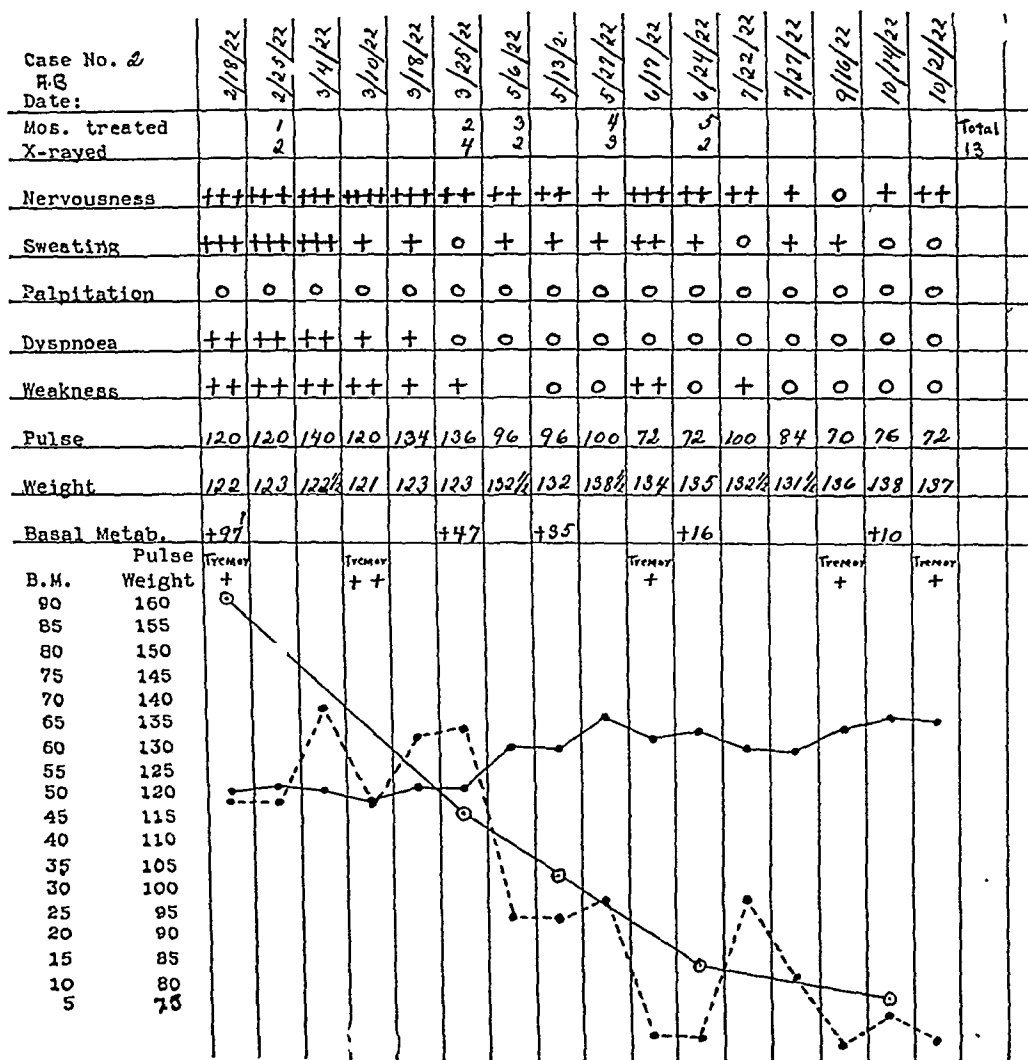
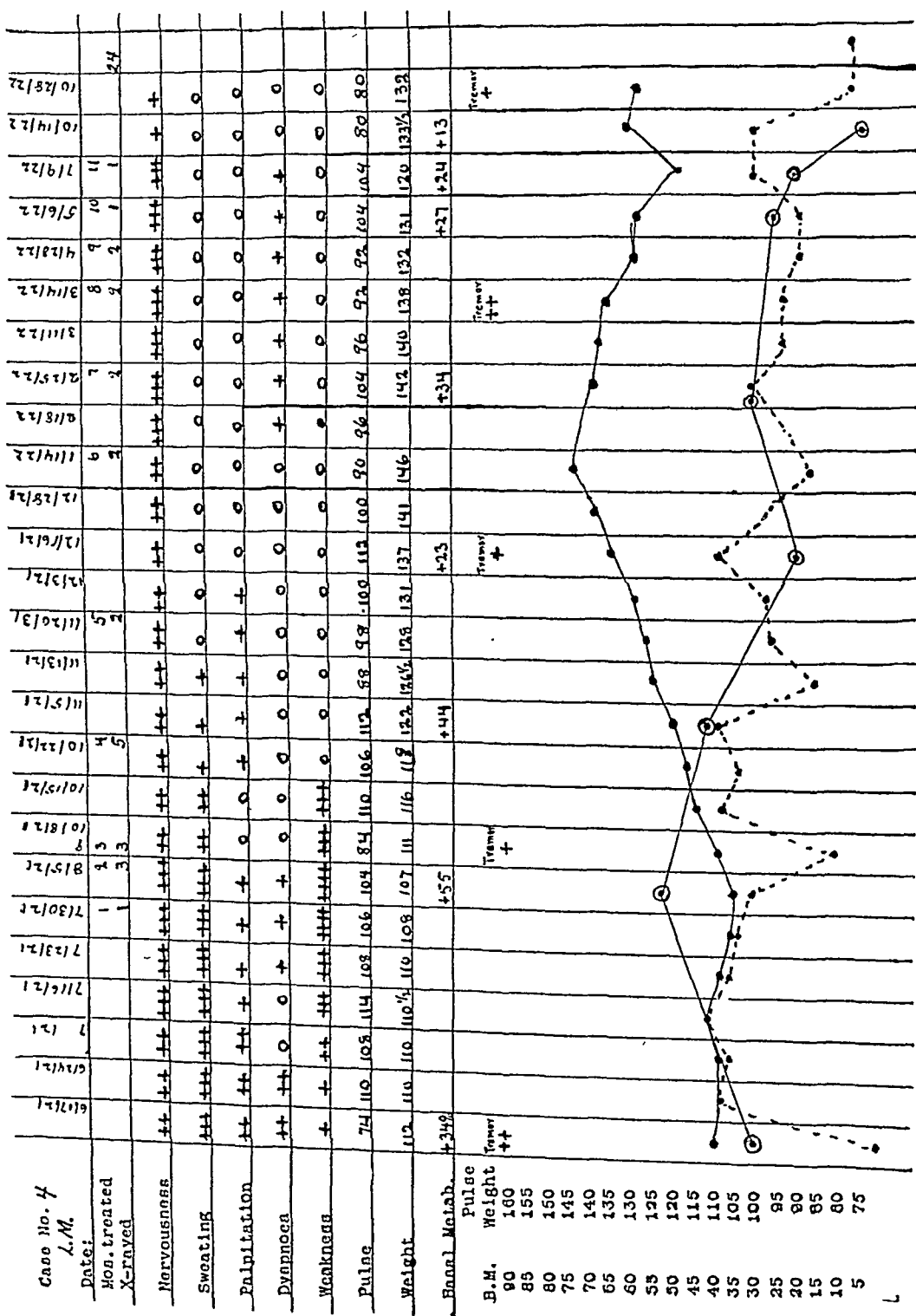


CHART 2

With the rising weight curve they all show a declining metabolism curve, which in each case has fallen to normal limits. The pulse curves as a rule show a downward trend, but appear rather erratic as compared with the rather uniform trend of the weight and metabolism curves.

As regards the subjective symptoms in these cases, we are impressed first with the striking changes in their appearance and

casual observer they would appear normal save for a prominence of the eyes. On more careful observation they are still not normal individuals. There is a residual nervousness, which they admit, or which may be brought out by scolding for laxity in attendance



or by some similar trick. Some complain of occasional palpitation of the heart or some other symptom. But these are brought out by inquiry and are not complained of voluntarily.

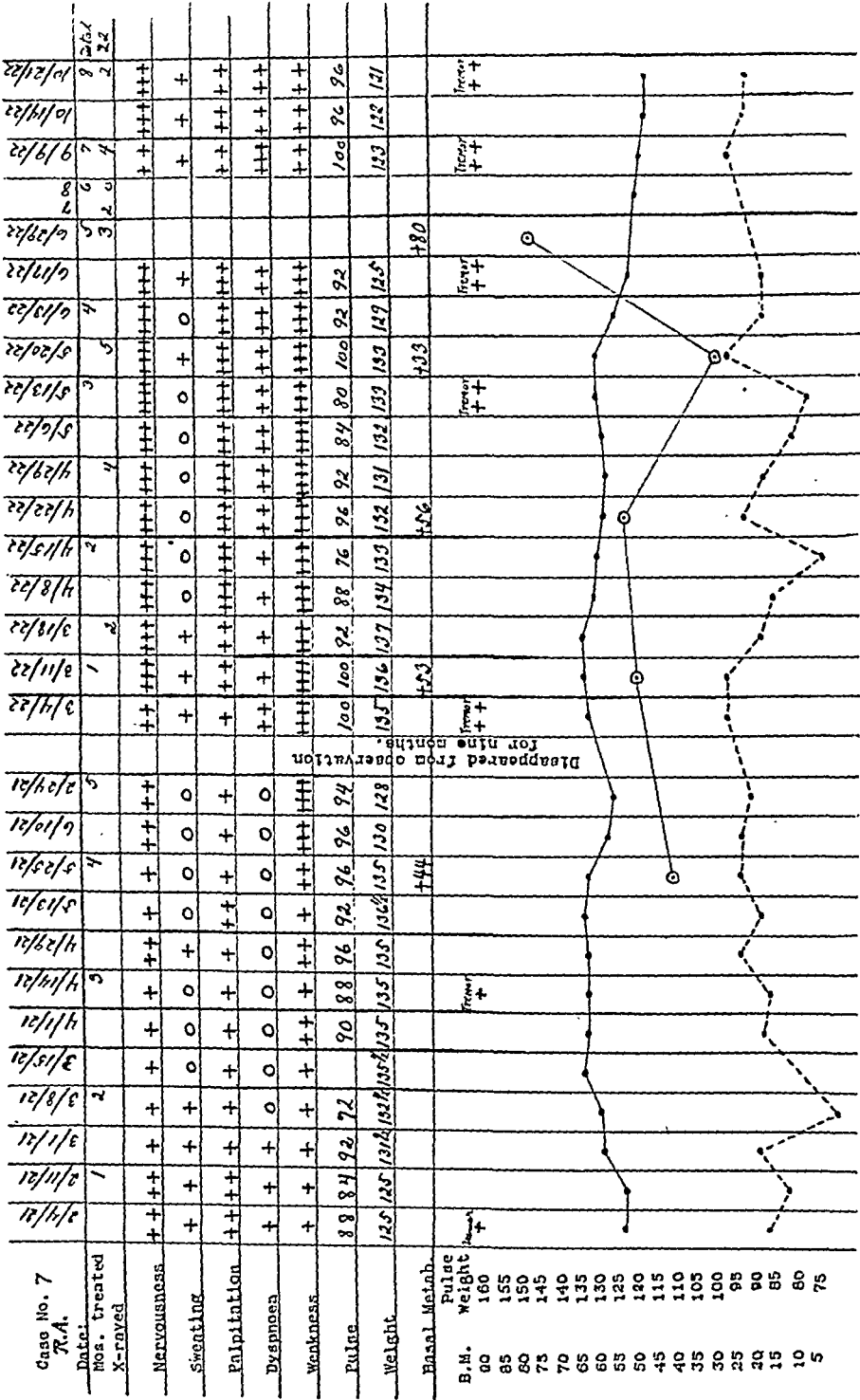


CHART 5

Under these circumstances then are these cases to be, at least temporarily, considered cured? Personally we are inclined to consider these results about as good as are to be expected in individuals who have once suffered from a severe thyroid toxemia. In the first place, they have probably been of a nervously unstable type before the onset of their toxemia, and in the second place, it is probable that any individual, who has once suffered from such a toxemia, will always retain the imprint of it in one way or another. This is true whether it terminates spontaneously or is interrupted by some special type of therapy.

As will be seen from their charts improvement in these cases has been a matter of months. Usually it has been five months before there has been any impressive change. Graves' disease is a disease which shows a tendency to run its course in cycles of remission and exacerbation. Indeed, Kessel, Lieb and Hyman have recently reported a series of cases in which no other treatment was instituted than rest in a hospital ward. Twenty-nine of these cases showed increases in metabolism comparable to those shown in the cases here reported. In most of these cases they report a spontaneous fall in the metabolic rate in from three to fourteen months. They do not report the changes in weight and pulse-rate; nor do they give any detailed report of the changes in subjective symptoms. From the standpoint of metabolism, which is the only standard of comparison which we have with their series of cases, one might infer that the influence of roentgen-ray therapy in our own cases was doubtful. While this is possible we are reluctant to admit it for several reasons. In the first place, the weight increase in these cases was so striking that we hesitate to consider it simply as the result of a natural remission of symptoms. In fact, the weight increase in some of the cases has been so marked as to suggest a change from the hyper- to the hypothyroid state. Our own cases were never ideally situated in a hospital ward for any considerable length of time, although 3 of them were hospitalized for from three to five weeks. Patient IV had been ill for two years before coming under treatment, and after six months felt better than at any time since the onset of her illness. Patient IX was responding well to treatment with falling metabolism and rising weight when she was forced to interrupt treatment. She went to the country for six months, where she held an easy job and where things were made easy for her. Upon her return her condition was practically the same as at the time she discontinued treatment. The influence of treatment here seems to be quite as definite as that seen in successful surgical cases, although perhaps not so prompt, and for the same reason. The surgeon mechanically removes a portion of the gland, and with roentgen-ray a portion of it is destroyed. If the theory of spontaneous remission holds, then all surgical results must be thrown out.

Granted that the improvement in these cases is the result of the influence of roentgen-ray therapy, we feel that they speak well for this type of treatment. We have not had these cases under observation for a sufficiently long period to speak concerning the most important criterion of the efficacy of any type of therapy, namely, the permanency of benefit. In the Thyroid Clinic new cases frequently appear who give a history of having had various operations performed; ligations, lobectomies, and sub-total resections. Their usual history is that for some time after operation they were improved, and then perhaps after some nervous stress or some infection, there was a return of all previous symptoms. We shall be interested in following up these cases and hope to report at a future time whether or not the improvement was temporary or permanent.

If the results be permanent, what are the advantages and disadvantages of this type of treatment? The disadvantage which first suggests itself is the length of time required to produce results. From an economic standpoint such a time-consuming method must appear to a distinct disadvantage as compared with successful surgery which terminates the toxemia more abruptly. Two of these cases after six months have developed cardiac arrhythmia (premature contractions), which we interpret as an evidence of myocardial injury resulting from their toxemia. These cardiac irregularities were noticed first when their conditions in other respects seemed much improved. The question has occurred to us as to whether this myocardial injury might not have been prevented had the toxemia been terminated more quickly. The obvious advantage as compared with surgery is the absence of operative risk. In the roentgen-ray dosage used in these cases we have seen no immediate alarming results. As regards the remote effects, 2 cases have come under our observation, not in this series, who have developed hypothyroid symptoms with metabolism of -28 per cent, and -30 per cent, after a course of roentgen-ray treatments for hyperthyroidism. This change however is one that is seen after surgery or may even occur spontaneously.

Turning now to the remaining cases in the series, Patient VI is interesting in that there has been marked subjective improvement, whereas the objective symptoms have changed very little. Within two months and after 4 treatments this patient's subjective symptoms had largely disappeared. At present she says "she feels fine." Her eyes are less prominent, and her tremor, though still present, is much less marked. There has been no increase in weight of any moment. Her heart was fibrillating on admission and had probably done so for some time previously. On continuous digitalis therapy there has been a reduction in rate. Her basal metabolism showed appreciable reduction in rate in the

early months of treatment, but has never fallen below 34 per cent in spite of the impression she gives now of the absence of toxicity. Her cardiac condition may account for this persistently high metabolism, but she presents no evidence of decompensation.

Cases VII and VIII have not been influenced by this treatment. Case VII received a total of 22 treatments, a larger number than that given the previous favorable cases. In spite of this her symptoms were uninfluenced. She lost 14 pounds in weight, and her metabolism increased. She finally became discouraged and requested an operation. A sub-total resection was done, and it is interesting to note that while the gland was adherent to the surrounding structures, the operative technic was not rendered particularly difficult by the previous radiation.

Unfortunately in this method of treatment the opportunity for studying the pathology of the glands in successfully treated cases does not present itself. In this case in which roentgen-ray therapy was unsuccessful, but in which prolonged treatment was employed, we were interested to see what changes, if any, had occurred in the gland which might be interpreted as the result of radiation. The following is the report of the anatomical changes in the specimen in this case by Dr. L. C. Knox:

Macroscopical examination: The specimen consists of the greater portion of both lobes of the thyroid gland. One measures $3.5 \times 2.5 \times 2.5$ cm., the other $3.5 \times 3 \times 3$ cm. Both are smoothly encapsulated anteriorly, are firm, clay-colored, finely lobulated, and appear cellular as no macroscopical follicles and no colloid can be made out on inspection. The parenchyma has a somewhat granular, homogeneous appearance.

Sections from various portions of the thyroid show no normal follicles and little normal epithelium, but a diffuse parenchymatous hyperplasia and hypertrophy which conforms to one of the types of gland seen in exophthalmic goiter. The gland is divided into small lobules by connective tissue which contains a few small collections of lymphocytes, but true lymphoid nodules with proliferating centers are not seen. There is no evidence of an increase in the amount of the small connective-tissue septa.

Relatively few acini contain colloid. This, in about half of the acini, stains homogeneously with eosin and so resembles the normal, but many of the follicles are empty and still others filled with a delicate reticulum or vacuolated acidophile material as though the secretion had varied from the normal in consistency, if not in reaction (see Fig. 1).

The epithelium of the follicles varies greatly in arrangement and morphology. In some areas they are cuboidal with central nuclei and are fairly regularly arranged in a single layer, but desquamating cells are numerous; the cell walls are frequently broken down and the cytoplasm fragmented. This is a rather prominent feature in

all of the sections and although a degenerative alteration, it cannot be assumed to be a postmortem change in view of the accurate preservation of the other structures. The nuclei vary in size and shape. Most of them are slightly larger than normal, but some are several times normal, are hyperchromatic, and irregular in outline. Mitoses are not found. Papillary outgrowths of epithelium are not numerous and when they are found are small, consisting of a low nodule of cells which only partially fills the lumen. The solidly cellular areas are apparently due rather to an increase in the number of small follicles than to a filling of the larger ones with papillary masses.

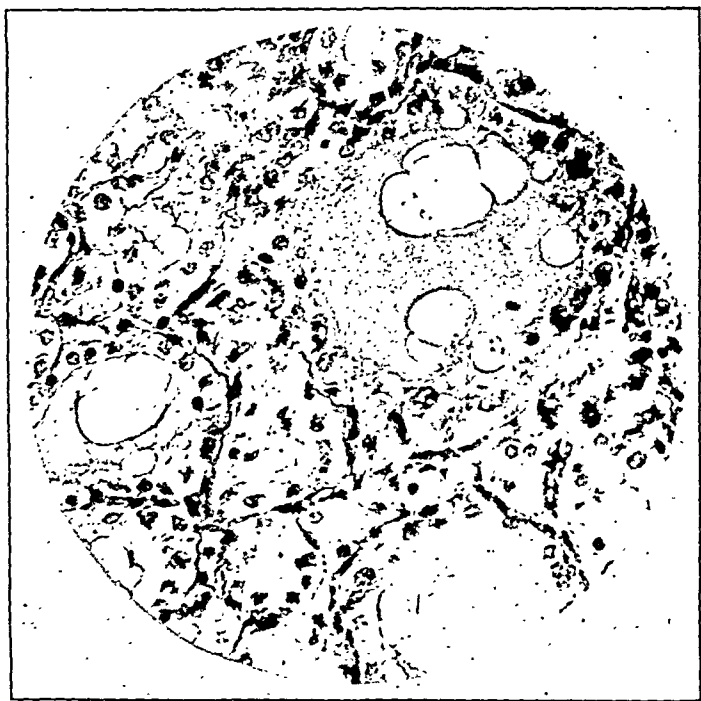


FIG. 1.—High power ($\times 400$) photomicrograph of exophthalmic goiter showing small lumina of the follicles with absent or vacuolated colloid.

As a whole there is less increase in the total cell content, less simple hypertrophy and better preservation of follicles than is often seen in exophthalmic thyroids. The nuclei also, while large, possess no more, and possibly fewer, anaplastic characteristics than are often seen.

The bloodvessels are inconspicuous in the more delicate ramifications of the stroma, but the larger branches of the arteries and veins are apparently normal and show no morphological lesions which can be attributed to the action of roentgen-ray. The absence of dilated capillaries is, however, noteworthy, for the gland, although hyperplastic, is notably lacking in this respect, and the question may properly be asked as to whether the pro-

longed roentgen ray has some vasomotor effect which inhibits congestion and capillary dilatation, a state which is an almost constant feature in exophthalmic goiter.

In this unsuccessfully treated patient, then, which had received 22 exposures of the dosage described above, no very definite changes which might be ascribed to the roentgen rays were found on microscopical examination. The most notable pathological finding was the absence of dilated capillaries which are found rather constantly in goiters of this type.

Case VIII has had 34 treatments in all. At the beginning of treatment there seemed to be distinct improvement, and again later for a period of three months he seemed to be doing well, but the improvement was temporary and at present his symptoms remain severe.

Considering these two cases as refractory to roentgen-ray therapy, we have tried to distinguish in them characteristics which would differentiate them from the other cases which have responded favorably. This we have been unable to do. In the duration of symptoms, in the severity and character of the subjective symptoms, in the pulse and the metabolic rates, there is nothing to distinguish them from the other cases.

No conclusion can be drawn from Case IX because her treatment had to be interrupted. Attention is drawn to the fact that she was improving up to the time her treatment was stopped, and that after six months her symptoms had changed very little.

Summary. In this report we include 9 cases of toxic exophthalmic goiter treated with roentgen-ray. In 5 of these cases the results of treatment have been satisfactory. In 1 case the influence of treatment is doubtful, and in another no conclusion can be drawn because treatment was interrupted. In the 2 remaining cases the toxemia seemed to increase in spite of prolonged treatment. In the 5 favorable cases we are unable as yet to speak of the permanency of benefit or tendency to recurrence of symptoms.

CASE REPORTS.

A summary of each of these 9 cases follows:

CASE I.—B. K., a married female, aged thirty-eight years, had had symptoms for six months.

Chief Complaint: Nervousness; moderate exophthalmos; marked tremor; diffuse smooth swelling involving the isthmus and both thyroid lobes. On admission the pulse-rate was 88; best weight, 155 pounds, six years before admission; weight on admission, 124 pounds. Roentgen-ray treatment was begun in August, 1921. She had 18 treatments in all during the next five months. Her weight increased 17 pounds while being treated, and has increased

24 pounds since; total increase in weight since admission, 41 pounds. Basal metabolism on admission was +63 per cent; at present +4 per cent. She is now free from symptoms, except that she perspires freely. The exophthalmos has disappeared and no tremor is present. In January, 1922, the patient had an acute respiratory infection with complicating otitis media with rupture of ear drum. At this time there was an increase in symptoms, but these quieted down when the infection subsided.

CASE II.—A. B., a married female, aged twenty-three years, whose occupation was that of a housewife, caring for household and two children, without help. Duration of symptoms on admission, four months.

Chief Complaint: Nervousness; marked exophthalmos; moderate tremor; diffuse smooth swelling involving the isthmus and both thyroid lobes. The pulse-rate on admission was 120; best weight, 145 pounds, four months before admission; weight on admission, 122 pounds. Roentgen-ray treatment was begun February, 1922. She had 11 treatments in next five months and the weight increased 13 pounds during treatment and has increased 2 pounds since. Basal metabolism on admission was +97 per cent, but at this time her nervousness made a satisfactory test difficult and this figure may not be reliable. After 11 treatments her metabolism had dropped to +16 per cent, and is now +10 per cent. Exophthalmos is still present, but much less marked; patient still has a slight tremor, and is nervous under stress. General condition is much improved and says herself that she feels fine. In March, 1922, she was admitted to the hospital for rest in bed for three weeks, and after this she went to a convalescent home for two weeks. In May, 1922, she was admitted to the hospital because she was two months pregnant, and a therapeutic abortion was performed. During the rest of the time she remained at home caring for her household and two children under school age.

CASE III.—R. L., a single female, aged twenty-four years, a domestic, the duration of whose symptoms was four months.

Chief Complaint: Nervousness; marked exophthalmos; moderate tremor; diffuse smooth swelling involving both thyroid lobes and the isthmus. The pulse-rate on admission was 108; best weight 135 pounds one year before admission; weight on admission, 119 pounds. Roentgen-ray treatment was begun January, 1922. She received 14 treatments in the next five months. The weight increased 5 pounds while under treatment and has increased 22 pounds since; total increase in weight, 27 pounds. The basal metabolism fell from +55 to +14 while under treatment, and is now 0. Patient continued occupation as a domestic except for a month between January 21 and February 21. At the present time

her exophthalmos is still present but much less marked. Tremor still present, but slight. She still complains at times of dyspnea, palpitation and nervousness, but is much stronger and does her work without fatigue. Cardiac rhythm was always regular until last visit when premature contractions were noted.

CASE IV.—L. M., a married woman, aged thirty-six years, the duration of whose symptoms extended over two years.

Chief Complaint: Palpitation of the heart; marked exophthalmos; marked tremor. The pulse on admission was 74; best weight, 160 pounds seven years before admission; weight on admission, 112 pounds. There was a diffuse smooth swelling of both thyroid lobes and isthmus. Roentgen-ray treatment begun July, 1921. She had 24 treatments covering a period of eleven months. Her basal metabolic record is as follows: On admission, +34 per cent; August, 1921, +55 per cent; December, 1921, +23 per cent; February, 1922, +34 per cent; October, 1922, +13 per cent. Her weight increased 39 pounds in the first six months of treatment, fell off 20 pounds in the next five months, and since then she has regained 12 pounds. Total weight gained since admission, 20 pounds. During the first six months of treatment patient's six-year-old daughter was sent to her grandmother to be cared for, but patient continued to do her housework for herself and her husband. In the summer of 1922 she was subjected to additional work and anxiety by the illness of a sister. During this time she lost much weight. After this she went to the country and was without household cares for six months, when she again gained in weight. At present she is much stronger and no longer complains of fatigue. Exophthalmos is still present, but much less marked, and there is a moderate tremor. She is still nervous under stress but complains of no other symptoms.

CASE V.—As this was a private patient, married, aged thirty-five years, admitted to the service of another member of the attending staff, although we have had the opportunity to observe her course, we have not as accurate a history of her disease as we have in the other cases. Duration of her symptoms before admission was about six months.

Chief Complaint: Palpitation of the heart; marked exophthalmos; moderate tremor. Diffuse smooth swelling of both thyroid lobes and isthmus. The pulse-rate on admission was 96. She was admitted to the hospital in March, 1922, where she remained for one month at rest in bed. She then returned home to her household and children with instructions about resting, which were poorly followed because of her lack of help in the household. Roentgen-ray treatment was begun in March and continued for the next five months, during which time she had a total of 16 treatments.

She gained 2.5 pounds while under treatment, but has gained 20 pounds since, making a total gain of 22.5 pounds. Her metabolism on admission was +75 per cent. This fell after two weeks of rest in bed to +30 per cent, but rose again while still at rest to +46 per cent. On leaving the hospital it rose to +66 per cent, but since then has fallen and is now +12 per cent. At present the patient says she "feels fine." She still becomes nervous under stress, has mild cardiac palpitation occasionally, and there is a questionable tremor. Her cardiac rhythm had always been regular until her last visit, when premature contractions were noted. This patient, in the fall of 1921, before coming under our observation, had had a rest cure of about six weeks in a sanatorium. She improved while at rest, but her symptoms returned to the same degree on returning home.

CASE VI.—G. H., a married woman, aged thirty-one years, the duration of whose symptoms was four years.

Chief Complaint: Marked exophthalmos; moderate tremor; heart fibrillating; apex rate on admission, 140; diffuse smooth swelling of both thyroid lobes and isthmus. She was admitted to thyroid clinic October, 1921, after leaving hospital, where right chest was aspirated for a pleurisy with effusion. The basal metabolism on admission was reported as +90 per cent, but conditions were not satisfactory and this result was questionable. After this her basal metabolic record was as follows: January, 1922, +57 per cent; February, +46 per cent; April, +46 per cent; May 6, +46 per cent; May 20, +53 per cent; June, +46 per cent; October, 34 per cent. The metabolism in this case has never returned to normal despite the fact that her subjective symptoms have disappeared. The metabolism may have been influenced by the cardiac condition, although the patient took the test satisfactorily after the first one, and there have been no evidences of cardiac decompensation. The pulse-rate noted on the chart is really the rate of the cardiac beats taken at the apex. Throughout the course of her observation she was given 4 digitan tablets a week. Patient's subjective symptoms improved markedly in the first two months of treatment. During the last eight months she insisted that she was well. A tremor is still present. Exophthalmos is present, but less marked. She was given 22 treatments over a period of eleven months. There has been no weight increase such as occurred in the previous cases, and in spite of the subjective improvement the metabolic rate has remained well above the normal.

CASE VII.—R. A., a housewife, aged forty-two years, who had had symptoms for twelve years.

Chief Complaint: Precordial pain; marked exophthalmos; marked tremor; diffuse smooth swelling of both thyroid lobes and isthmus.

The pulse-rate on admission was 88. She was admitted to thyroid clinic February 4, 1921. Roentgen-ray treatment was advised, but patient failed to follow advice. She was sent to the country for three weeks with some improvement of symptoms and a gain in weight of 10 pounds. She was lost sight of in June and did not return to the clinic until March, 1922. From then on she took roentgen-ray treatments faithfully and had 22 treatments in eight months. There was no improvement in subjective symptoms; her weight decreased steadily and she lost 14 pounds in all. Her metabolism fell from +53 to +33 per cent, and rose again to +80 per cent. She became discouraged and was anxious for an operation. She was admitted to the hospital and after two weeks' rest in bed her metabolism measured +30 per cent. There had been an interval of five months since the last rate of 80 per cent had been obtained. She was operated on by Dr. F. S. Mathews. At operation there was a loss of elasticity of the tissues of the neck. The thyroid was adherent to the surrounding tissues, but the adhesions were separated easily and the operative procedure was not rendered especially difficult by the previous roentgen-ray treatments.

CASE VIII.—O. H., a married male, aged forty-four years, the duration of whose symptoms was nine months.

Chief Complaint: Nervousness; marked exophthalmos; marked tremor; diffuse smooth swelling of both thyroid lobes and isthmus. The pulse-rate on admission was 94; best weight, 175 pounds ten months before admission; weight on admission, 167 pounds. The patient was admitted to the hospital and remained at rest in bed from January 9 to February 1. During this time he was given 5 roentgen-ray treatments. On discharge he was much improved. He was admitted to the thyroid clinic in March, 1922. All of his symptoms were severe. From March until October there seemed to be a gradual improvement. At this time all of his symptoms became worse with a rising metabolic rate. While his weight is 10 pounds higher than on admission to the hospital his symptoms are severe, and he has derived little benefit from his treatment. In all he has had 34 roentgen-ray treatments.

CASE IX.—E. T., a single woman, chambermaid, had had symptoms for thirteen months.

Chief Complaint: Mental depression; marked exophthalmos; marked tremor; smooth swelling of left thyroid lobe measuring 6 x 4 cm. The pulse-rate on admission was 124; best weight, 112 pounds nine years before admission; weight on admission, 96 pounds. This patient was admitted to one of the surgical wards in April, 1921, with all the symptoms of a severe thyroid toxemia. Basal metabolism, +75 per cent. After rest in bed the metabolism

drooped to +43 per cent, when a right lobectomy was done. She improved after this, but on January 1, 1922, she returned complaining of prominent eyes and swelling of the neck. Her metabolism at this time was +19 per cent. A second operation was done with the removal of the isthmus and part of the left lobe. Symptoms increased after the operation and her metabolism rose to +47 per cent at the end of a month. She was admitted to the thyroid clinic in February, 1922, with the symptoms of a moderately severe toxemia. Symptoms continued severe for the next two months with rising metabolic rate, then improvement began and the patient seemed to be doing well. Four months after treatment was begun her employer left for the country and patient had to discontinue treatment. For the next six months she worked as a chambermaid, but with very light work. After six months' absence she returned to the clinic feeling, she said, much improved, but without having increased in weight and with a marked tachycardia and with a metabolic rate the same as when treatment was discontinued.

SPOROTRICHOSIS.

BY HARRY R. FOERSTER, B.S., M.D.,

MILWAUKEE, WIS.

UNKNOWN twenty-five years ago, considered a rare disease until the last decade, sporotrichosis has come to be recognized as a mycotic disease of foremost importance and of considerable prevalence. In this country, however, it is still generally regarded as being more of academic interest than of practical importance and it is probably overlooked more frequently than recognized. Most of the reported cases have been of one classical type permitting of ready clinical diagnosis and have been recorded in one section of the country shortly after several pioneer clinical papers and presentations had awakened a special interest in this disease.

Economic Importance. Considering the frequency of mycoses, a knowledge of sporotrichosis is of importance because the similarity of this disease to common forms of tuberculosis, syphilis and indolent pyogenic infections renders it easily overlooked and failure to recognize it often leaves in its wake a trail of serious misfortunes for the patient, whereas recognition leads to a speedy cure. Undoubtedly, under erroneous diagnoses, many cases of sporotrichosis go through protracted periods of therapeutic mismanagement during which the afflicted individual suffers not only the worry, disability and occasional serious illness caused by the disease, but also pecuniary loss, sometimes loss of employment and

the stigma attached to diagnoses of tuberculosis and syphilis, the latter often accompanying the patient through life because of the cure of the sporotrichosis accomplished by the iodide medication prescribed for syphilis.

Gougerot¹ cited a case of sporotrichosis in which the patient was cured in six weeks with potassium iodide after having had 4 unsuccessful operations for osteomyelitis during three years of hospitalization. He recorded also 2 cases of double amputation of the thighs, an arm amputation, a nephrectomy because of a diagnosis of pyelonephritis, and a case of suspected glanders in which extensive cauterization with the production of severe disfigurement was followed by recurrence of the sporotrichosis elsewhere. Occurrences of this nature contrast sharply with the good results attainable when sporotrichosis is recognized. The diagnosis is not difficult to establish and the treatment is simple.

The economic importance of sporotrichosis is indicated by the preponderance of cases in manual workers in whom its occurrence interferes with their livelihood. This disability, when the disease is not recognized promptly or is erroneously diagnosed, results in considerable expense to either the individual, the community, the employer, the workman's aid society or the insurance company through prolonged invalidism or accidental permanent disability. The following statistics refer to cases reported in the United States:

Of 70 adults where the records indicated the occupation, there were 20 farmers and farm laborers, 16 industrial laborers, 18 housewives and servants, 5 gardeners, 3 florists, 2 clerks and 1 of each of the following: woodsman, soldier, sailor, merchant, teacher and shop superintendent.

The average age of 100 cases was twenty-nine years, 71 having occurred between the ages of sixteen and fifty. The oldest was seventy-seven years, the youngest sixteen months; 20 were children. There were 67 males and 33 females.

In 109 cases the site of the primary lesion was indicated as follows: Thumb, 9; index finger, 13; other fingers, 11; back of hand, 17; hand, 8; palm, 4; wrist, 10; forearm, 10; arm, 2; elbow, 3; shoulder, 2; neck, 2; cheek, 1; toe, 2; foot, 1; leg, 9; eye-lids, 5. Skin injuries, most of them occurring in line of work, were mentioned as predisposing factors in 43 cases and in only a few cases was an absence of recognizable injury stated. The foregoing figures indicate the importance of this disease as an occupational dermatosis, most of the cases having occurred at the ages of maximum productive capacity among manual workers, chiefly wage earners, and having involved parts of the body, the disease of which would naturally have caused impairment of efficiency and a variable amount of disability. The location of the primary lesion on the hand or finger, most frequently the right, in 62 and on some part of the upper extremity in 90 of 109 cases, and the frequency with

which a preceding trauma has been recorded, indicate a distinct occupational factor in the acquisition of the disease.

History and Distribution. In 1896 a St. Louis iron-worker, in reaching into a keg of red lead, scratched his index finger on a nail. Shortly afterward a small abscess appeared at the site of injury followed by the development of a number of indurated and in part ulcerated nodules along the course of the radial lymphatics. The disease being refractory to routine surgical management and the patient being incapacitated for work during a period of three months, he returned to his home in Baltimore and came under the observation of Finney and Schenck. The latter isolated a fungus from the lesions by culture, which was classified as of the genus *sporotrichum* by E. F. Smith. The subsequent report² of the latter in association with Schenck stands as the first recorded case of sporotrichosis.

In 1899, Brayton³ reported the case of a florist who, following a finger prick with a wire, developed a clinically similar condition. Unfortunately no cultural diagnosis was made. In 1900, Hektoen and Perkins⁴ reported a case in a boy, aged five years, following a blow on the finger with a hammer. The causative organism was isolated by culture, found to be identical with the one isolated by Schenck, and was designated by them *Sporotrichum schenckii*.

In 1903, de Beurmann and Ramond⁵ recognized the first case of sporotrichosis in France, and the organism isolated was studied by Matruchot and Ramond, and in 1905 named by them *Sporotrichum beurmanni*. In 1906, 2 additional French cases were recorded by de Beurmann and Gougerot⁶ and 1 by Dor. Isolated cases were reported in America by Stickney in 1905. Duque⁷ (in Cuba) in 1908, Burlew, Trimble and Shaw, and Pusey in 1909, R. L. Sutton, Hyde and Davis,⁸ Zurawski, Gifford, Stelwagon and Stout in 1910.

R. L. Sutton,⁹ of Missouri, and Trimble and Shaw,¹⁰ of Kansas, are credited for the local interest aroused in this disease in 1910, which resulted in the recording of 39 cases, 21 of them proved by culture, in their section of the country in the following two years. The thorough studies of de Beurmann and Gougerot,^{11, 12, 13, 14} to whom we owe most of our knowledge of sporotrichosis, are responsible for the hundreds of cases recorded in France, where this disease is considered of economic and of great practical importance.

In 1907, Lutz and Splendore,¹⁵ in Brazil, recognized spontaneous sporotrichosis in the rat and reported a human case. Balino and Marco del Pont reported a case in Argentine and Greco in Uruguay. In 1908, Carougeau¹⁶ discovered the disease among mules and horses in Madagascar, where it is quite common. Page, Frothingham and Paige,¹⁷ studying epizootic lymphangitis in horses, isolated an organism identical with the sporothrix and established the identity of this disease with sporotrichosis.

Sporotrichosis is of world-wide distribution, having been recorded as occurring in Europe, the Americas, Asia and Oceanica. Its frequency in certain areas such as the Missouri River basin, rural France and Madagascar cannot be entirely attributed to special efforts directed toward its discovery and is probably due to environmental and endemic characteristics. Of 125 cases of sporotrichosis reported in the United States, in 66 of which the causative organism was isolated, 94 occurred in the Middle West. North Dakota is credited with 26; Nebraska, 15; Kansas, 14; Oklahoma, 11; Wisconsin and Missouri, 9 each; Illinois and Indiana, 6 each; Texas, 5; South Dakota, 4; the others are scattered. Reudiger²⁷ and Hamburger²⁸ have both commented on the concentration of many of the western cases in the Missouri River Valley and the prevalence of the disease among farmers. Very few cases have been recorded in the eastern United States, England and Germany. Adamson,¹⁸ of London, saw his first case in 1911, and that in a man recently returned from Brazil. The first recognized case originating in England was seen by this same observer¹⁹ in 1913; the first case in Scotland, by Walker and Ritchie,²⁰ in 1910; the first in Ireland by Beatty²¹ in 1917. The first case recorded in the German literature was reported by Stein,²² of Berne, in 1909. A second Swiss case, reported by Hugel,²³ in 1913, came from Alsace. Other early cases were recorded in Germany by Arndt,²⁴ in 1910, and by Fielitz; in Austria-Hungary by Krenn and Schrameck²⁵ in 1909 and by Hecht²⁶ in 1913; in Spain by Oyarzabel and Peyri; in Italy by Campana, Vignolo-Luttati and Curuccio; in Turkey by Hodara and Fuad Bey; in Belgium by Lerat; in China by Tyau.

Etiology and Pathogenesis. The causative organism of sporotrichosis is a fungus of the genus *Sporotrichum*. It is of widespread distribution as a saprophyte in Nature and is pathogenic to plants as well as to man and lower animals. A hardy fungus, it grows in Nature on all sorts of soil and at a wide temperature range, having been found in the Alps and in the tropics, and on bark, thorns, wild plants, flowers, grasses, vegetables and vegetable debris. Its occurrence in man is usually through the contamination of a slight wound with infected plant or vegetable matter, though it can undoubtedly make its entry through the unbroken mucous membrane and by way of the hair follicles. Several cases have been reported among vegetable venders and chair and basket weavers; it has occurred at the site of a cut from a potato peeler, following injury while wiring flowers and plants, after injury while handling mouldy boards, and by infection from soiled dressings of cases of sporotrichosis. Three of my cases followed punctures with the thorns of the barberry bush, and a fourth a bruise on the hand while handling these shrubs. Saint-Girons reported a similar mode of infection.

It has also been reported as contracted from animals. Cases have been recorded among farm hands and stable boys, in several of which instances there were evidences of the horses cared for having been afflicted with disease, usually diagnosed glanders. Carougeau's¹⁶ case of a veterinarian infected after operating on a mule having sporotrichosis, Meyer's²⁹ accidental inoculation of a finger with laboratory material from an infected horse, with the development in both cases of typical human sporotrichosis, and similar cases following the bite of a gopher having a cutaneous disease, and the bites of rats, a parrot, a hen, a field mouse and a white mouse are evidence of the likelihood of direct animal transmission, though it may be argued in some of these cases that the wounds may have been secondarily inoculated by plant matter. The development of the parasite on flies, ants and wasps has led de Beurmann to suggest the possibility of inoculation by insect bites.

Another avenue of infection is the gastro-intestinal tract which may be invaded through minute abrasions or through the unbroken mucosa and account for some cases of obscure origin. Such infection can occur from eating raw or insufficiently cooked vegetables and fruits. De Beurmann and Davis³⁰ have each shown experimentally the permeability of the intact mucosa to the sporothrix. The organisms are carried through the intestinal wall by the migratory phagocytes, such infection tending to localize in the mesentery, peritoneum and spleen.

De Beurmann and Gougerot have shown the sporothrix to occur as a saprophyte in the human pharynx and have recorded the development of the disease following cutaneous inoculation of abrasions by means of the saliva in a "carrier" of the infection. Following inoculation the sporothrix may remain localized or may be disseminated by way of the lymphatics or the blood stream. Many cases occur in subjects of tuberculosis or in convalescents and the infrequency of its occurrence in other members of a family, where exposure to contamination is likely, suggests the probable failure of inoculation because of the normal resistance of the healthy organism.

It is apparent that the sporothrix, a fungus of low virulence, requires a suitable soil for its development as a pathogenic agent and that the disease, sporotrichosis, probably develops in most cases because of a condition of lessened resistance in the host at the time of inoculation.

Symptomatology. Sporotrichosis is an infectious granulomatous disease invading at times any or all tissues and organs of the body and showing great clinical polymorphism. It is, therefore, of importance not only to the dermatologist but to all engaged in the practice or study of medicine. In a given case of sporotrichosis there may be cutaneous, subcutaneous and osseous or visceral

lesions, lesions in different stages of evolution or involution and lesions of tuberculoid, syphiloid, ecthymiform or trichophytoid type. This polymorphism of lesions is frequent and constitutes a diagnostic sign. Even a single lesion may show mixed characters, one segment appearing tuberculoid, another syphiloid. Gougerot¹ recognizes the following clinical varieties:

I. MULTIPLE DISSEMINATED SUBCUTANEOUS GUMMOUS SPOROTRICHOSIS. This is the variety de Beurmann considers the most common, and is characterized by the insidious development of small, hard, elastic and painless subcutaneous nodules varying in number from four or five to about thirty or even more than a hundred, showing no selective localization or systematic grouping, attaining sometimes the size of walnuts and rapidly undergoing softening with the formation of cold abscesses in the course of three to six weeks. The softening occurs superficially and centrally, yielding a cup-shaped depression with marginal induration to the palpating finger. These abscesses adhere to the skin, develop without inflammation, pain or systemic symptoms and remain quiescent, while new lesions appear and go through a similar course of evolution. These gummas ulcerate but rarely, unless incised, in which case a thin viscid pus is evacuated, which later becomes thick and purulent and following which the incision closes with reformation of the abscess, or as a result of the incision a syphiloid ulcer develops with persistent discharge and crusting or with a tendency to cicatrization and formation of a fistula. In such cases the adjacent skin is sometimes infected and cutaneous lesions appear. This form of sporotrichosis, sometimes called the syphiloid variety, is distinguished from the subcutaneous gummosis syphilides by the larger number of lesions, the rapid softening without inflammation, the resistance to mercury and the infrequency of involvement of the mucous membranes or regional lymph glands. Syphilitic gummas seldom form large abscesses, ulcerate with greater regularity and show more or less circular ulceration with infiltrated margins and no undermining of the edges.

II. MULTIPLE ULCERATING GUMMOUS SPOROTRICHOSIS. This variety of the disease develops similarly to the first but ulcerates with the development of tuberculoid, syphiloid or ecthymiform lesions. The ulcerations are usually fistulous in character, with narrow, irregular openings, loose violaceous borders, scanty serous or viscid sanguinolent pus, and dirty granular bases that bleed readily and are usually crust covered. The cup-shaped depression with peripheral infiltration already referred to can usually be palpated. This, the most common, is the tuberculoid type. Sometimes there are large open crateriform ulcers of the syphiloid type. Occasionally the ulcerations are superficial and heavily crusted like the lesions of ecthyma. Frequently there are several fistulae from

one abscess, their orifices separated by narrow bridges of violaceous skin. The development of the ulcerative stage may be rapid, occurring in less than three weeks, or it may require several months. Involution is usually very slow in untreated cases, ulcerations persisting for months or even years. The scars are usually irregular, linear or stellate with associated tongue-like tags or remaining fistulous walls, and with areolar pigmentation. Sometimes the scars are smooth, polycyclic and pigmented as in syphilis, at other times they show central keloidal thickening as in tuberculosis. This type of sporotrichosis is differentiated from scrofuloderma by the central superficial softening, the wide violaceous zone of infiltration, the homogeneous, viscid pus, the rapid evolution of individual lesions, the lesional and evolutionary polymorphism and the absence of lymph-node enlargements and scrofulodermatous scars and fistulae in the neck. Of diagnostic importance is the recurrence of ulceration within the scars after spontaneous healing or inadequate treatment. While general symptoms are ordinarily absent, in long-continued, ulcerative cases there is usually a steadily increasing debility, anemia and cachexia and some local disability. Eisenstaedt³¹ reported the first case of tuberculoid sporotrichosis in this country in a patient operated upon for supposed tuberculous adenitis of the neck, with subsequent development of disseminated cutaneous lesions.

Rarely a "hot" abscess will develop with associated edema and inflammation, simulating a furuncle. Autoinoculation may occur about the ulcers with the development of acneiform, vegetating or verrucous, and occasionally trichophytoid lesions.

III. LOCALIZED LYMPHANGITIC SPOROTRICHOSIS. This variety of the disease is the one most commonly met with and described in American literature. The first manifestation is the initial lesion or sporotrichotic chancre, occurring at the site of inoculation, where there is usually a break in continuity of the skin due to injury. A frequent site is the index finger, thumb or back of the hand. This lesion is sometimes a simple ulcer, an acneiform pustule, an abscess, a gumma or frequently a vegetative plaque, becoming verrucous and having the appearance of a verrucous tuberculosis. Rarely this is the only lesion present. Usually after a variable period of a few days to several weeks multiple subcutaneous gummas appear along the course of lymphatic drainage from the site of inoculation, and with these there is also frequently an ascending lymphangitis resulting in a palpable, painless, cord-like thickening of the lymphatic vessels, which is sometimes very pronounced. The gummas usually behave in a similar manner to the lesions in the first variety of the disease, but frequently ulcerate spontaneously or after incision with the development of polymorphous lesions such as have just been described. The regional lymph nodes may enlarge, being indurated and occasionally sup-

purative. A pure culture of sporothrix has been obtained from a suppurative gland. The lymphatic variety remains a localized cutaneous and subcutaneous process, very rarely becoming disseminated through the lympho-vascular system to other parts of the body. The initial lesion may have healed, the disease showing only the localized gummatous lymphangitis, or there may be no lymphangitis and the site of inoculation may show the only manifestation of the disease. The diagnosis is based on the mixed aspect of the chancre, which at one time may be both vegetating and oozing, verrucous and dry, the rapid evolution of the lesions, the presence of micro-abscesses in the vegetations and of intradermic abscesses, the frequency of autoinoculation of the adjacent skin, the polymorphism of the gummas and their lymphatic distribution, the lymphatic cords, the lack of symptoms and finally the rapid response to potassium iodide.

IV. SPOROTRICHOSIS DERMIQUE. This comprises a group showing ulcerated or non-ulcerated lesions, nodules or infiltrated plaques, folliculitis, weeping, fungating, verrucous or papillomatous lesions, simulating in its varying forms verrucous tuberculosis, papulo-necrotic tuberculides, scrofuloderma, blastomycosis, sarcoid, papulo-ulcerative and crustaceous syphilides, acnes and epitheliomas. A diagnostic feature in these cases is the usual presence of small gummas and micro-abscesses in association with the lesions.

Our third case, several months after spontaneous involution of all visible lesions, showed a recurrence with the formation of a vegetative plaque on the flexor surface of the right wrist. This lesion was a sharply defined, oval granuloma, reddish-brown in color, and its surface was studded with drops of creamy pus from numerous miliary abscesses. The lesion was typical in appearance of a common form of blastomycosis, but a pure culture of sporothrix was obtained from it in six days. Examination of smears for blastomycetes was negative and the lesion healed rapidly under potassium iodide.

Hugel's²³ case gave a history of an extensive pustular acne of ten years' duration which had become considerably worse after sleeping in fields and woods some months previously to being seen. He showed the usual picture of a severe acne of the chest and back, with lesions on arms, legs and abdomen as well, and lentil to hazelnut-sized nodules, ulcers, fistulæ and scars, and viscid, reddish-yellow pus. It was the picture of acne cachecticorum, as described by Kaposi, and was so diagnosed until the sporothrix was cultivated from an incised nodule. The histological picture was like that in sporotrichosis, and the nodules and ulcers disappeared after four weeks of potassium iodide medication. We have seen an identical case in a farmer boy in whom a mycotic infection was suspected after failure of therapeutic

response, but the case was lost sight of and no bacteriological examinations had been made.

V. SPOROTRICHOSIS EPIDERMIQUE. In this group are lesions resembling erythematous-squamous dermatitis, vesicular eczemas, trichophytides and tinea kerion, frequently developing through inoculation of the skin by secretions from ulcerated sporotrichoses.

VI. EXTRACUTANEOUS SPOROTRICHOSIS. As previously noted, sporotrichosis may involve any and all tissues of the body. Usually in these cases, but not invariably, there are also cutaneous lesions.

The *mucous membranes* may be involved by erythematous, ulcerative, suppurating, vegetative or papillomatous lesions with the development of angina, stomatitis, glossitis, laryngitis and rhinitis. These lesions are usually accompanied by lymphangitic gummosis chains or adenopathy, do not show false membranes and on healing leave soft, pliable scars without deformity. On the mucous membranes in such healed cases the sporothrix may grow as a saprophyte, rendering the patient a typical "carrier" of the disease. Our fifth case, in addition to cutaneous lesions, showed a sharply defined, cup-shaped ulceration of the mucosa overlying the anterior part of the nasal septum which had the appearance of an ulcerative syphilide.

The *muscles*, the *mammary glands* and other *glandular structures* may be involved with lesions usually resembling syphilitic gummas or tuberculous "cold abscesses," pyogenic abscesses and even carcinoma. Gougerot describes as one of the seven varieties of sporotrichosis "le grand absces," occurring as single or multiple subcutaneous, muscular or osseous abscesses containing 500 cc or more of serous or viscid pus. This variety was first described by Dor,³² in 1906, and is attributed to a distinct species of sporothrix, the *Sporotrichum dori*. The *bones* may be involved, with osteomyelitis and hypertrophic osteitis, simulating luetic, tuberculous, chronic pyogenic or metastatic malignant conditions and accounting for spontaneous fractures and interosseous abscesses. Aloin and Vallin reported a case of sporotrichotic abscess of the frontal bone simulating a tertiary syphilide. Sporotrichosis of the *synovial membranes and articulations* may resemble conditions of tuberculous, gonococcal or syphilitic origin. Wolbach, Sisson and Maier³³ described a case of acute traumatic arthritis from which they isolated a distinct species of sporothrix, the *Sporotrichum councilmani*.

Gifford and Wilder and McCullough³⁴ have reported a number of cases of *eyelid* infection. The conjunctiva in such cases shows follicular granulations and minute yellowish gummas and the sporothrix may be cultivated from the lacrimal secretions. McCullough acquired a conjunctival infection while working with laboratory cultures.

The *viscera* may be infected by the sporothrix. Le Blanc³⁵ reported 2 pulmonary cases, in 1 of which the sporothrix was cultivated from the sputum. Cases of pulmonary involvement are recorded also in the French literature. Warfield³⁶ recently reported a case of extensive visceral involvement with cultural and necropsy findings. The patient was a stable boy, whose first lesion was on the dorsum of the foot. Disseminated cutaneous and subcutaneous lesions appeared later, then pulmonary symptoms, and the patient grew progressively worse and died in spite of intensive iodide medication. Brainos³⁷ reported a sporotrichotic chancre of the penis, diagnosed primary syphilis, which became phagedenic under antiluetic treatment, then yielded a positive culture of sporothrix and healed rapidly under potassium iodide. Cases of sporotrichotic epididymoöorchitis and of pyelonephritis have been reported.

Acute and Subacute Febrile Sporotrichosis. While sporotrichosis is characterized by the extreme indolence of its development and course and the absence of fever and all systemic symptoms, it may at times be abrupt in onset with fever and the general symptoms of an acute septicemia and a rapidity of development of lesions in the manner of an eruption. Cases have been recorded in which febrile attacks and constitutional symptoms attended the development of acutely inflammatory abscesses. Some showed a tendency to recrudescence of febrile symptoms coincident with the formation of new lesions, or a tendency to become subacute and protracted with progressive asthenia, loss of weight, anemia and general debility. Occasionally a gumma takes on the character of an acute coccic abscess with rapid development, adherence to the skin, lancinating pain, edema, diffuse, red infiltration of an erysipeloid type, ulceration in a few days and then chronic involution. Cultures in such cases fail to show secondary infection and do not always yield the sporothrix.

The case of Brissaud and Rathery¹³ is worth citing because of its resemblance to a pyogenic bacteriemia. The first symptom of the disease was a diffuse pain in the forearm followed shortly by the appearance of a swelling on the arm and later a nodule, small at first and attaining the size of a walnut. Similar lesions then appeared on the legs, all preceded by diffuse pain. Fever developed, alternating at times with chills, and there was continuous nausea, anorexia, epistaxis and insomnia. In three weeks the patient lost 20 pounds, became asthenic and unable to work, and entered the hospital with a diffuse generalized eruption of hypodermic sporotrichotic gummas and a temperature of 101° to 102.2° F., which remained so for eight days, the fever terminating by lysis on the eighteenth day. During three months in the hospital the patient had a second febrile attack, similar to the first, associated with the appearance of crops of new lesions with ulceration

and sanguineous discharge. Cure finally resulted under prolonged iodide medication.

Pathological-histology. The microscopical study of a sporotrichotic lesion reveals it to be a chronic granuloma showing similarity to syphilitic, tuberculous and chronic pyogenic disease all in one lesion. The periphery shows an intense connective-tissue inflammation with vascular dilatation and infiltration of plasma cells, young connective-tissue elements, lymphocytes and some mast cells, concentrated about the vascular structures in sheath-like formation but also invading the collagen bundles. In the mid-portion there are numerous large epithelioid cells and fairly abundant giant cells of the Langerhans type with a grouping suggestive of tubercles. Within these cell groupings are polymorphonuclear neutrophiles and eosinophiles, macrophages and erythrocytes, especially dense near the center, where there is a variable amount of necrosis and suppuration. There is a greater tendency to the formation of micro-abscesses than to necrosis and necrotic elements are mingled with richly stained cells. Thus we see three zones: The periphery syphiloid, the middle tuberculoid and the center chronic suppurative. These zones vary in distinctiveness and cannot always be defined. In syphilis the vascular changes are usually more pronounced, the epithelioid and giant cells show less grouping, the polymorphonuclear cells are less abundant and there is no suggestion of a fibrous encapsulation. In tuberculosis the infiltrate is less rich in cellular elements, the necrosis is more pronounced and compact, the vascular changes are more intense and the periphery is less sharply defined. Frequently a differential diagnosis from syphilis, tuberculosis or blastomycosis cannot be made. The cutaneous lesions show chronic inflammatory changes of the epidermis and corium with minute papillary abscesses and the vascular and perivascular reactions and tubercle formations previously noted.

It is difficult to find the organism in human tissue though easy in experimental animals. Basophilic, spindle-shaped spore forms are found at the periphery of the lesion and sometimes in the giant cells. The mycelium cannot be demonstrated in tissue sections.

Morphology and Bacteriology. The sporothrix is a filamentous, spore-bearing fungus, recognized as occurring in several varieties. Probably because of the pleomorphic characteristics of this fungus there has been a great deal of controversial discussion over the identity of the organisms causing the common varieties of sporotrichosis, the French¹⁴ holding out for a distinction between *Sporotrichum beurmanni* and *Sporotrichum schenckii* and maintaining the fungus most commonly met with to be the *Sporotrichum beurmanni*, while the American cause has been ably championed by J. D. Davis,³⁸ who has shown these two species to be identical and

who believes that only the name *Sporotrichum schenckii* should be retained in honor of the priority of Schenck's discovery. Less common species of pathogenic sporotricha are the *Sporotrichum dori* and *Sporotrichum councilmani*. The *Sporotrichum indicum*, *Sporotrichum jeanselmei*, *Sporotrichum gougeroti* and *Sporotrichum asteroides* are recognized as subvarieties of *Sporotrichum beurmanni*, with the possible exception of *Sporotrichum gougeroti*.

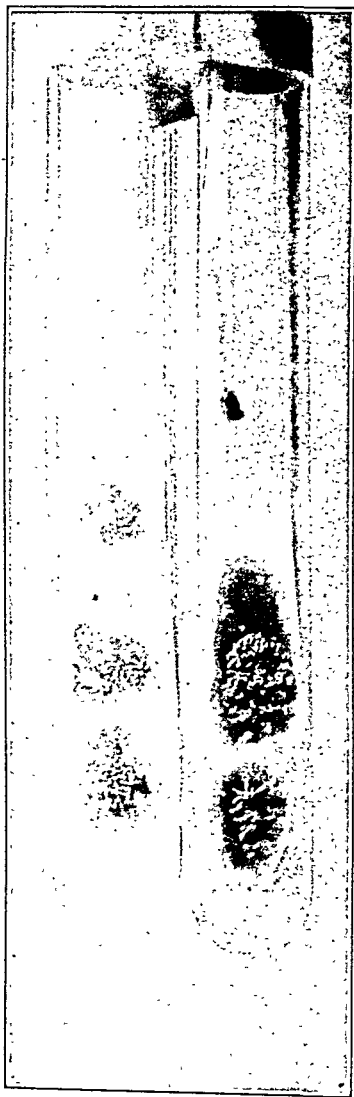


FIG. 1.—Three- and six-week cultures of *Sporotrichum schenckii*.

The sporothrix is difficult to find in smear preparations, but is usually readily grown on ordinary culture media. A liberal amount of pus, preferably aspirated from an unopened abscess, is planted on the culture medium, of which the best is probably potato or Sabouraud's peptone-glucose agar: Peptone, 1; glucose, 3.7; agar, 1.5; water, 100. The tubes are kept uncapped at room

temperature and in four to eight days colonies appear as small white acuminate points about 1 mm. in diameter and surrounded by white finely rayed areolæ. The colonies slowly increase in size and assume a convoluted appearance aptly described by Beatty as resembling worm casts in the sands at the seashore. After a variable time, usually seven to ten days, sometimes three or more weeks, the colonies darken in color, becoming light brown, chocolate-brown and finally black.

Davis³⁹ has shown chromogenesis to be a variable characteristic of all strains and dependent on growth conditions. Pigment formation is more abundant on rich sugar media, especially on carrots, and when the oxygen supply is good. The mycelium is colorless or a faint brown, the pigment is in the spores, which are aërobes, and is light brown, homogeneous and non-granular. Meyer and Aird⁴⁰ showed variable fermentation of lactose and saccharose by both French and American varieties. Growth characteristics at different temperatures are also variable.

For studying a culture, Beatty²¹ advises placing a small amount on a slide and gently spreading it in water so as not to disturb the spores. When dry, a few drops of formic acid are applied, the slide heated until the acid steams, then cooled, and this process repeated several times, after which the slide is washed, counterstained for several minutes with borax methylene blue, washed, dehydrated with absolute alcohol and mounted in xylol. The mycelium is septate and branching and about 2 microns in diameter. The spores are pear-shaped, 2 to 4 microns wide, 3 to 6 microns long, mounted on short slight stems and usually grouped at the ends or on branches of mycelium. Growth takes place by elongation and division of spores and subsequent development of radiating mycelium. After long growth or on media poor in nutrient value, chlamydospores appear at the ends of filaments or along their course. These are thick-walled spherical bodies, about 5 or more microns in diameter.⁴²

In living tissue the sporotricha occur always as elongated or oval bodies of fairly uniform size, about 2 to 3 microns broad and 3 to 5 microns long. They are usually single, but may be grouped radially about a spore or end to end. These spindle forms are basophilic and often show transverse, dark, granular bands, clear areas at the ends and a capsule-like membrane. Growth takes place by budding from the ends. To demonstrate the organisms in tissue, Taylor⁴¹ recommends a modified Gram stain. The sections are steamed for one minute with aniline methylene violet and counterstained lightly with alcoholic eosin. Direct preparations from lesions show Gram-negative spores, while from artificial media Gram-positive and acid-fast spores and mycelium are obtained.

The true pathogenicity of the sporothrix has been demonstrated by the fulfilment of Koch's postulates. Acute and subacute septicemias are usually produced in all experimental animals with diffuse involvement and degeneration of the viscera as well as cutaneous and subcutaneous lesions. In pathogenicity in animals and in serological reactions the *Sporotrichum schenckii* and the *Sporotrichum beurmanni* are similar.

The studies of de Beurmann, Gougerot, Bloch, Widal and Abrami have indicated the similarity of mycotic to bacterial infections. The differences are largely differences of degree and detail. Both types of organisms occur as saprophytes in Nature, and in man and animals are pathogenic under certain conditions, gain entrance to the body by cutaneous or mucous membrane inoculation, produce disease because of either diminished resistance of the soil, augmentation of virulence of the parasite, sensitization of the soil by secretions of the saprophyte, or adaptation of the soil to the germ, and are subject to hematogenous or lymphatic dissemination.

Serology. In sporotrichosis there is frequently a hematogenous dissemination of the infection and the spores have been isolated from the circulating blood. Widal and Abrami⁴³ introduced the *agglutination test* as a diagnostic factor, the technic of which is similar to that used in typhoid fever and is diagnostic in dilutions of 1 to 100 and over. They obtained agglutination at 1 to 800, and a year after cure de Beurmann obtained positive reactions at 1 to 60 and 1 to 80. Gaucher obtained a sudden agglutination increase from 1 to 800 to 1 to 1500 dilution just preceding a relapse with multiple gummosis skin lesions apparently the result of a sporotrichemia. Normal human serum may give an agglutination as high as 1 to 40, while some cases of sporotrichosis give negative tests with undiluted serum. Various mycoses give positive reactions in dilutions of 1 to 40 to 1 to 150, and occasionally even higher, a reaction of 1 to 400 having been recorded in hemisporosis. The technic is given by Moore and Davis.⁴⁴ A two to four weeks' old culture of sporothrix is shaken down in normal saline solution, then centrifuged to separate the spores from the mycelium which settles to the bottom. The suspension of spores is diluted so as to obtain several hundred spores to a microscopical field. This is then mixed with the serum in varying dilutions and read microscopically after twenty-four hours.

Widal and Abrami also introduced the *complement-fixation test*, based on the ready formation of antibodies in sporotrichotic serum and affording a valuable diagnostic aid in differentiating blastomycosis which apparently does not generate antibodies. A culture of sporothrix is used as the antigen for this reaction, which is negative for syphilis, tuberculosis, blastomycosis and tinea infections, but

may be positive for hemisporosis, actinomycosis, and thrush as well as for sporotrichosis.

Diagnosis. In the diagnosis of sporotrichosis, syphilis, tuberculosis, pyogenic infections, glanders, lepra, blastomycosis, actinomycosis and other mycoses come up for consideration. The recognition of sporotrichosis is largely dependent upon a consideration of the possibility of its presence in all cases of chronic suppurative or granulomatous disease. This is especially important when such cases are characterized by multiple cutaneous or subcutaneous gummosis lesions often associated with a primary traumatic lesion and a distribution suggestive of lymphatic dissemination, by the absence of the usual inflammatory symptoms of a coccic infection, by the failure of response to ordinary surgical procedures and by the protracted nature of the disease. A large number of disseminated cutaneous or subcutaneous gummas with lack of a characteristic distribution or grouping, absence of adenopathy and mucous membrane lesions and absence of other evidences of syphilis should arouse a suspicion of sporotrichosis. Whenever there are multiple suppurating lesions in bones, joints, muscles or synoviae, particularly when such lesions follow the course of the lymphatics from a peripheral ulcerating lesion, sporotrichosis must be considered.

Polymorphism in a solitary lesion or group of lesions and peculiarities in evolution or involution of cutaneous or subcutaneous suppuration, such as failure of an abscess to ulcerate, continued abscess formation after an ulcer has cicatrized and the appearance of neighboring lesions after apparent lymphatic dissemination or epidermal autoinoculation, are diagnostic features. It must be kept in mind that the basic lesion of sporotrichosis is the gumma, that this lesion always begins as a small hard nodule, and when it softens or ulcerates the process is always central with a remaining peripheral infiltration resulting in a characteristic cup-like lesion. The ulceration is usually smaller than the infiltration, the pus is usually viscid or sanguino-purulent, there is never a "core" as in a furuncle, the ulcer margins are violaceous and ragged and the cicatrices imperfect. The sporotrichotic lesion may be solitary, it may be tender and acutely inflammatory, or the disease may manifest itself as an acute bacteriemia.

Sporotrichosis may occur in a syphilitic and frequently does occur in tuberculous patients, and it may be associated with other cutaneous or extracutaneous diseases. Potassium iodide should not be used in a therapeutic test for syphilis, nor iodide preparations in suspected tuberculoses, when the possibility of a sporotrichotic infection exists.

Recourse to culture should always be taken for the sporothrix grows on ordinary sugar media at room temperature and is easily

recognized. When cultures fail, due to secondary infection or iodide medication, the agglutination test or the complement-fixation reaction should be employed. Another test is the *intracutaneous reaction* of Bloch, in which 0.1 cc of a killed saline suspension of sporothrix is injected into the skin.⁴⁴ In positive cases a small, raised papule with an edematous and inflammatory areola appears after twenty-four to forty-eight hours, while the control inoculations are negative. The administration of potassium iodide does not interfere with the intradermic reaction but may result in a weak agglutination reaction. An eosinophilia of 5 to 8 per cent or more and the presence of large numbers of eosinophiles in the pus are of diagnostic value.²⁵ There may be a leukocytosis of 16,000 to 20,000. The most satisfactory experimental inoculation is that of the rat in which an early sporotrichotic orchitis develops. Other diagnostic features have been referred to under symptomatology and pathological histology.

Treatment. Potassium iodide is practically a specific in the treatment of sporotrichosis, though it probably has no direct lethal action on the organism and its administration as a prophylactic does not prevent infection. It should be given in rapidly increasing dosage of from 30 to 90 grains daily with plenty of water or milk, and it should be continued for four to six weeks after apparent complete recovery to avoid recurrence of the disease. If potassium iodide is not tolerated, autogenous vaccines, potassium iodide with tincture of belladonna and arsenicals are recommended. Stokes, Nichols and Reasoner have had favorable results with arsphenamine. Stokes has noted response under mercury, while Crutchfield reports failure of mercury and arsphenamine to influence the lesions. Surgical intervention, such as incision, excision, cautery or curettage, is distinctly contraindicated and is usually followed by increased suppuration and prolonged ulceration. Open lesions should be flushed and compressed, and large abscesses aspirated and flushed with Lugol's solution (iodine, 10; kali iodide, 20; aqua, q. s., 100). For local application, Gougerot recommends: Potassium iodide, 4; ferric iodide, 4; emplastra diachylon, 60. For torpid ulcerations he suggests the application of tincture of iodine followed by the application of a powder of morphine chloride, 0.5; powdered iodine, 0.5; talc, 60. Hecht²¹ employed vaccines in his case with rapid healing after seven injections, but recurrence in six months. The roentgen-rays and ultraviolet rays have been used with success to hasten resorption of lesions.

Prognosis. The prognosis, as a rule, is good, for under appropriate treatment prompt improvement and rapid recovery may be expected in four to eight weeks or at the most in several months' time. However, some patients decline steadily in spite of treatment and recover only after a very stormy course or die from

intercurrent disease. Relapses or recurrences should be guarded against by prolonged iodide medication.

CASE I.—H. S., a white male, aged twenty-two years, was an employee of a tree nursery. This patient and the three following were referred by a liability insurance company.

The patient stated that in April, 1922, he injured the tip of the right thumb with a barberry thorn while at work. In a few days the thumb is said to have swelled to twice its normal size, showing a granulomatous mass with multiple pustules at the tip and along the nail folds. At about the same time a pea-sized subcutaneous nodule appeared on the back of the hand and a week later a group of symptomless nodules appeared in linear formation along the right forearm. About ten days later some of these nodules enlarged and softened with inflammatory changes in the overlying skin.

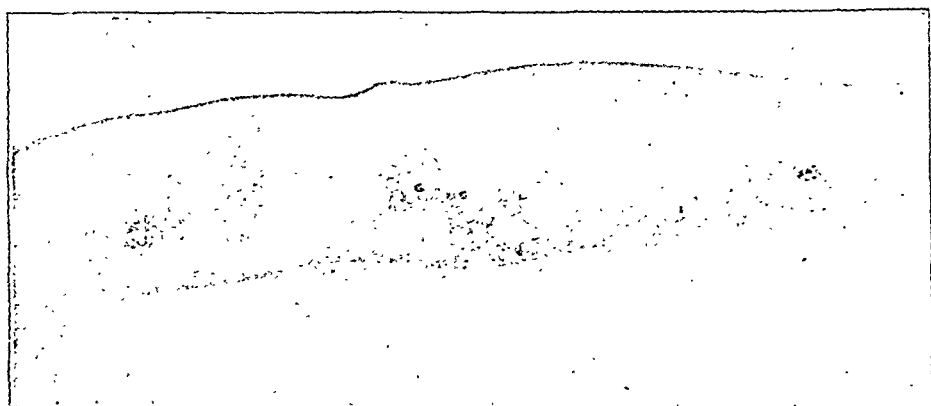


FIG. 2.—Ulcerative lymphangitic sporotrichosis. (Case I.)

The abscesses were then incised, following which they enlarged and continued to discharge pus. Several abscesses ulcerated spontaneously. I saw the patient on July 7, at which time he showed a condition as described, though the primary lesions had healed and there were gummas along the lymphatics of the right upper arm, enlarged lymph glands in the right axilla and a discoid, ulcerated and infiltrated area of inflammation, 2 cm. in diameter, on the flexor surface of the right forearm. The history and examination were otherwise negative. A softened nodule was incised and in eleven days a pure culture of sporothrix was obtained from the pus on glucose-peptone agar. Under 90 grains of potassium iodide daily the ulcerations healed in four weeks and the nodules gradually disappeared in the course of two months.

CASE II.—L. M., a white male, aged sixteen years, was also an employee of a tree nursery. Early in June, 1922, the patient

injured the back of the right hand with a shovel while at work. A few days later the site of the abrasion showed an inflammatory ulceration and a week later several pea-sized nodules appeared on the back of the hand, wrist and forearm in the order named. At the end of the second week an inflammatory cutaneous nodule appeared on the right shoulder and ulcerated spontaneously in several days. The patient recalled a past furunculosis on the back and neck; the history was otherwise negative. Examination on July 6 showed a sharply defined ulceration, 1 cm. in diameter, with marginal infiltration and a seropurulent discharge on the back of the right hand. The right deltoid area showed a ragged, superficial ulceration about 2 cm. in diameter. At the elbow there was a small, deep ulcer with deep infiltration extending longitudinally as a narrow band. There were several pea-sized cutaneous and subcutaneous nodules and an enlarged epitrochlear lymph



FIG. 3.—Sporotrichotic granuloma resembling blastomycosis. (Case III.)

gland. Culture media inoculated with pus remained negative, but an abscess opened by Dr. Margot, pathologist at the Milwaukee County Hospital, yielded the sporothrix. The lesions rapidly involuted under large doses of potassium iodide and a local application containing thymol iodide. The patient was returned to work eleven days later, at which time all the ulcers had healed and involution was progressing rapidly.

CASE III.—F. R., a white male, aged fifty years, was a gardener at a tree nursery. Patient stated that while trimming barberry hedges in May, 1922, he injured the left thumb and right index finger with thorns which became imbedded in the skin. Ten days later these sites became swollen, pustular and granulomatous, causing total disability. Several weeks later nodules appeared on the flexor surface of the left forearm and extensor surface of the right forearm. Examination on July 20 showed large granulo-

matous lesions on the thumb and index finger, and hazelnut-sized cutaneous and subcutaneous nodules on the forearms, associated with palpable thickening of the lymphatic vessels. Some of these nodules showed softening, but none had ulcerated. Patient stated he had had a similar condition of less severity about a year previously when on the same job. At that time the lesions yielded to a local application which he was again employing. I advised potassium iodide. I saw the patient again on December 1, 1922, at which time he presented himself because of a vegetative plaque on the flexor surface of the left wrist, 5 cm. in diameter and $\frac{1}{2}$ cm. in elevation, with a sharply defined elevated margin and a granulomatous surface studded with pustules. The present lesion had developed gradually during several months, and the previously noted lesions had entirely disappeared, though internal medication was not employed. As noted in the text, this lesion had the appearance of blastomycosis, though examination failed to confirm that suspicion, and a pure culture sporothrix was obtained from some viscid greenish-yellow pus expressed from the growth. Treatment had been withheld until the diagnosis was established, but when potassium iodide was administered involution was rapid and the patient was returned to work in a few weeks. This patient was shown at the annual meeting of the Chicago Dermatological Society on January 18, 1923.

CASE IV.—A. McL., a white male, aged fifty-four years, a gardener at a tree nursery, was admitted to the Surgical Service of the Milwaukee County Hospital in May, 1922, because of multiple suppurative lesions on the hands. The patient stated that early in May he removed several barberry thorns from the left index finger and several days later he bruised the back of the right hand. After about ten days the index finger became swollen and inflamed and the abrasion on the hand ulcerated. During the next week the left forearm became swollen. Several pure cultures of sporothrix were obtained by Dr. Margot. When I saw the patient, on July 6, he showed a recent scar on the left index finger, an irregular ulceration on the back of the right hand, subcutaneous and cutaneous gummous nodules in linear arrangement on both forearms, palpable cord-like thickening of the lymphatic vessels and several enlarged axillary lymph nodes. The only ulcerated nodules were those that had been incised. After two months of potassium iodide internally and local applications of Lugol's solution, the ulcerations had healed and the patient had returned to work, though evidences of the disease were still present.

CASE V.—A white male, aged thirty-one years, foundry foreman, was referred by Dr. A. J. Williams, of Waukesha, Wis. In March, 1922, the patient was burned on the flexor surface of the

right forearm with molten iron. Healing occurred in two weeks, leaving a scar. About three weeks later a pea-sized lump appeared next to this scar and ulcerated in two weeks, discharging a colorless, thin, sticky fluid. In two weeks this ulceration healed spontaneously and a week later two additional small pea-sized nodules appeared $\frac{1}{2}$ inch from the site of the burn and $1\frac{1}{4}$ inches from the previous ulcer. These lesions ulcerated in a week, discharging the same quality of fluid and then healing. Two weeks later a fourth nodule appeared 1 inch distant from the last two. In one week this lesion attained the size of a small pea, opened spontaneously, discharged a fluid pus and healed in five days. After remaining healed for one month this last abscess suppurated and ulcerated again and remained open to the time of examination. About the sixth month of the disease a fifth nodule appeared, developed to the size of a cherry in three weeks, opened, discharged and remained open, enlarging gradually and showing no tendency toward healing. These lesions had all been painless. A negative venereal history, a negative Wassermann test, and failure of response to germicidal and healing applications were reported. When I saw the patient for the first time on October 9, 1922, he showed the last two ulcers cited and the pigmentation and scarring of the previous lesions. There were no other cutaneous lesions, no enlarged lymph nodes and no palpable lymphatic vessels. Examination of the mucous membranes showed a deep, sharply defined, cup-shaped ulceration of the nasal mucosa, about 1 cm. in diameter, on the anterior portion of the septum on the left side. This lesion had the appearance of a syphilitic ulcer. There was no evidence of syphilis or tuberculosis. Pus taken from the ulcerations on the forearm was planted on Sabouraud's media, the patient placed on potassium iodide, 10 to 30 gm., three times a day, and the lesions exposed to the ultraviolet light. Response was rapid, the ulcerations on the arm having healed completely in four weeks and the nasal ulcer in five weeks. The cultures remaining negative, a specimen of blood was taken on December 2, at which time there was no evidence of the disease, though the patient was still taking iodide. The following findings were recorded by Dr Arthur Margot, to whom I am indebted for carrying out the complement-fixation and agglutination tests: Complement-fixation: Patient's serum, 0.1 to 0.2 cc; antigen, 0.1 to 0.5 cc; complement, 0.5 cc; physiological saline, 0.8 to 0.4 cc; sensitized cells, 1 cc. Result, ++ in all of six tests.

Agglutination Test. Positive agglutination was obtained in dilutions of 1 to 25, 1 to 50, 1 to 100 and 1 to 200; negative at 1 to 300. All controls were negative.

CASE VI.—J. B., a white male, aged twenty-one years, a fiber chair-weaver, of Waukesha, Wis., developed an infiltrated nodule

on the inner margin of the left forearm late in November, 1922. About two weeks later this lesion showed the characteristics of an indolent furuncle and opened, discharging a small amount of pus. During the next few weeks a chain of subcutaneous nodules appeared on the same forearm and arm. The patient was seen by me, January 16, 1923, through the courtesy of Dr. S. J. Seeger. Examination showed, at the site of the first lesion noted, a superficial ulcer, about 2.5 cm. in diameter, with a raised infiltrated marginal ridge and a pus-covered, granulating center. Above this ulcer, in linear arrangement along the course of lymphatic drainage, were eight subcutaneous gummas varying in size from that of a pea to a small hazelnut. These lesions were hard, elastic, freely movable and painless. There were also several palpable glands in the left axilla, but no other manifestations of the disease. There was no history of an associated injury. The gumma directly above the ulcer showed central softening and adherence to the overlying



FIG. 4.—Sporotrichotic chancre with gummous lymphangitis. (Case VI.)

skin, which showed a dusky red inflammation. This lesion was incised and the viscid greenish-yellow pus cultured on maltose-peptone agar. Seven days later colonies of *Sporotrichum schenckii* were identified and the patient placed on potassium iodide medication, to which he responded with healing of the ulcer and involution of the gummas.

Conclusion. In reviewing the histories of reported cases of sporotrichosis, one is impressed by the great frequency with which this disease is erroneously diagnosed and apparently not even suspected for weeks, months and sometimes years. During all this time the patient is partially or wholly incapacitated for work and subjected to medical and surgical attention that does not benefit him. The glaring deficiencies of diagnostic effort as disclosed by the records are irrefutable evidences in support of the view that numerous cases of sporotrichosis are never recognized. The frequency with which sporotrichosis develops following injury while at work, its occurrence chiefly among the wage-earning class of individuals, especially those in certain vocations, and the predi-

lection of the disease for the hands and forearms among manual workers are, I believe, arguments justifying its consideration among the groups of occupational diseases. The ever-widening scope of industrial and social medicine, enhanced by the introduction of special legislation in many states, increases the importance of such diseases. In four of my cases, employees of a tree nursery, settlement for compensation claims rested upon a recognition of the disease and its mode of contraction.

The evidence at hand indicates that sporotrichosis is a disease of considerable prevalence and of world-wide distribution with a tendency to endemic occurrence in certain localities where the frequency of its recognition appears to vary directly with the alertness of the medical profession to the possibilities of its presence. It is also evident that sporotrichosis is of considerable economic importance, and the rapidity and ease of cure under appropriate management, as contrasted with the otherwise prolonged period of disability and medical supervision, make it incumbent upon the practising physician and surgeon to acquaint himself with the various manifestations of this disease.

BIBLIOGRAPHY.

1. Gougerot: *La Dermatologie en Clientèle*, A. Maloine et Fils, Paris, 1919.
2. Schenck: *Bull. Johns Hopkins Hosp.*, 1898, 93, 286.
3. Brayton: *Indianapolis Med. Jour.*, 1899, 18, 272.
4. Hektoen and Perkins: *Jour. Exper. Med.*, 1900, 5, 77.
5. de Beurmann and Ramond: *Ann. de dermat. et syph.*, 1903, 4, 678.
6. Matruchot et Ramond: *Compt. rend. Soc. de biol.*, 1905, 59, 379.
7. Duque: *Am. Jour. Dermat. and Genito-Urin. Dis.*, 1908, 12, 240.
8. Hyde and Davis: *Jour. Cutan. Dis.*, 1910, 28, 321.
9. Sutton, R. L.: *Jour. Am. Med. Assn.*, 1910, 55, 1000 and 2213.
10. Trimble and Shaw: *Kansas Med. Jour.*, 1909, 9, 305.
11. de Beurmann and Gougerot: *Ann. de dermat. et syph.*, 1906, 7, 837.
12. de Beurmann and Gougerot: *Ann. de dermat. et syph.*, 1907, 8, 603.
13. de Beurmann and Gougerot: *Ann. de dermat. et syph.*, 1909, 9, 81.
14. de Beurmann and Gougerot: *Arch. f. dermat. u. syph.*, 1911, 110, 25.
15. Lutz and Splendore: *Centralb. f. Bakteriöl.*, 1908, 46, 21.
16. Carougeau: *Bull. et mém. Soc. méd. de hôp. de Paris*, 1909, 34, 507.
17. Page, Fröthingham and Paige: *Jour. Med. Res.*, 1910, 23, 137.
18. Adamson: *Brit. Jour. Dermat. and Syph.*, 1911, 23, 239.
19. Adamson: *Brit. Jour. Dermat. and Syph.*, 1913, 25, 33.
20. Walker and Ritchie: *Brit. Med. Jour.*, 1911, 2, 1.
21. Beatty: *Brit. Jour. Dermat. and Syph.*, 1917, 29, 270.
22. Stein: *Arch. f. Dermat. u. Syph.*, 1909, 98, 3.
23. Hugel: *Arch. f. Dermat. u. Syph.*, 1910, 102, 95.
24. Arndt: *Dermat. Ztschr.*, 1910, 17, 24.
25. Krenn and Schrameck: *Wien. klin. Wchnschr.*, 1909, 22, 1519.
26. Hecht: *Arch. f. Dermat. u. Syph.*, 1913, 116, 846.
27. Reudiger: *Jour. Infect. Dis.*, 1912, 11, 193.
28. Hamburger: *Jour. Am. Med. Assn.*, 1912, 59, 1590.
29. Meyer: *Jour. Am. Med. Assn.*, 1915, 65, 579.
30. Davis: *Jour. Infect. Dis.*, 1916, 19, 688.
31. Eisenstaedt: *Jour. Am. Med. Assn.*, 1918, 71, 726.
32. Dor: *Presse méd.*, 1906, 14, 234.
33. Wolbach, Sisson and Maier: *Jour. Med. Res.*, 1917, 36, 337.

34. Wilder and McCullough: Jour. Am. Med. Assn., 1914, 62, 1156. Gifford: Arch. Ophth., 1922, 51, 540.
35. Le Blanc: Illinois Med. Jour., 1920, 38, 516.
36. Warfield: Am. Jour. Med. Sci., 1922, 164, 72.
37. Brainos: Paris méd., 1920, 10, 247.
38. Davis: Univ. Wisconsin Studies in Science, No. 2, June, 1921, p. 104.
39. Davis: Jour. Infect. Dis., 1915, 17, 174.
40. Meyer and Aird: Jour. Infect. Dis., 1915, 16, 399.
41. Taylor: Jour. Am. Med. Assn., 1913, 60, 1142.
42. Davis: Jour. Infect. Dis., 1914, 15, 483.
43. Widal and Abrami: Ann. de l'Inst. Pasteur, 1910, 24, 1.
44. Moore and Davis: Jour. Infect. Dis., 1918, 23, 252.
45. Crutchfield: Arch. Dermat. and Syph., 1923, 7, 226.

AN UNUSUAL MALIGNANT TUMOR OF THE PANCREAS.

BY N. C. FOOT, M.D., B. N. CARTER, M.D.,

AND

M. J. FLIPSE, M.D.,

CINCINNATI, OHIO.

(From the Department of Pathology, Surgery and Medicine of the Medical College of the University of Cincinnati and the Cincinnati General Hospital.)

THE neoplasm to be described presented so much difficulty in diagnosis and the case such unusual symptoms, that it is well worth reporting. Regarded medically it was thought to be a case of cerebellar tumor or abscess; surgically considered it appeared to be the latter; owing to its gross pathology this opinion was at first substantiated, only to be rejected for a diagnosis of malignant neoplasm with cerebral and cerebellar metastases. The primary growth was apparently in or near the head of the pancreas, with metastases to the hilum of the right lung, the pericardium, retroperitoneal and mesenteric lymph nodes, and to the cerebrum and cerebellum by way of the choroid plexus. Owing to the fact that the primary growth, as determined by its larger size and more extensive necrosis, occurred in the head of the pancreas, and because there was a developmental defect in the adrenals, whereby they were firmly and inextricably attached to the kidneys, it was thought to be a neuroblastoma. The head of the pancreas might have become involved by direct extension from the retroperitoneal region and the metastases to the brain further strengthened the impression of neuroblastic origin.

Microscopical sections presented great similarity to neuroblastoma, excepting that the non-medullated neurofibrillæ and the rosettes usually encountered in these tumors were not to be found. There was a chance that the granular material lying between the

cells might be degenerated neurofibrillæ, or that the tumor represented the "neurocytoma" of Marchland (1907). In view of this uncertainty, microscopical sections from the growth were submitted to five eminent pathologists, all of whom have written more or less extensively upon the subject of neuroblastoma. Three of them confirmed the diagnosis, but admitted that it was difficult or impossible to prove it; the other two, living in different cities, were united in pronouncing it an atypical, extremely metaplastic carcinoma of the pancreas. For this reason we must give both sides of the question due consideration. It seems that the latter diagnosis is probably correct, after having reviewed the material most carefully and consulted the rather meagre literature on this type of pancreatic carcinoma.

We are all familiar with the more common primary carcinomata of the pancreas which arise from the duct epithelium and present no difficulties to pathological diagnosis, because of their outspoken epithelial type and glandular arrangement; the anaplastic type represented by the tumor we are describing, however, is rarely seen and as rarely reported. Articles on the subject are limited and unsatisfactory, if one disregards a few excellent, but brief reports. Perhaps the most instructive passages in this literature are contained in Ewing's (1922) article on carcinoma of the pancreas in his text-book on Neoplastic Diseases. He describes these tumors under two heads: (1) Carcinoma of the Ducts, and (2) Carcinoma of the Parenchyma. Fig. 331, on page 705, in his book, shows a tumor of the latter type, the photomicrograph of which might have been taken from one of our preparations. In substance Ewing states that this type varies greatly, the cells may be small or large, granular or hydropic, the cell-borders are often indistinct and the nuclei large in proportion to the size of the entire cell. The more embryonic type of these tumors is composed of cells which are still smaller and very diffusely arranged in an indefinite stroma, which may be very delicate, giving a faintly alveolar appearance to a neoplasm which otherwise might pass for a lymphosarcoma. He mentions one of his cases in which the original tumor was sarcomatous in appearance and the metastases to the lung contained small cuboidal, or fusiform cells. He briefly reviews the literature to the date of his publication (1922).

Aside from his description of this tumor, we have been unable to find many articles that have any bearing on our case. Lockwood (1921) describes a tumor in the tail of the pancreas, diagnosed by Black and Bloodgood as sarcoma. The photomicrographs resemble our case, although we do not question the diagnosis on such meagre grounds. Speed (1920) reviews the literature and has collected 11 cases, 3 of them showing lung metastases, but none extension to the brain. Liver metastases are more usual.

Fowler (1920) has described a carcinoma of the head of the pancreas in which the differentiation of the cells is very poor and the appearance of which compares somewhat closely with those of our tumor. The liver was invaded in this case, but neither lung nor brain. Goldstein (1922), reviewing the history of pancreatic sarcoma, quotes Segri, who found only 2 sarcomata in a series of 132 pancreatic tumors. He has been unable to find more than 19 accepted cases. Horgan (1920) discusses the histogenesis of carcinoma of the pancreas from cells in the islands of Langerhans. Fabozzi (1903) held this view and described 4 cases, 3 of which metastasized to the liver. His illustrations are too diagrammatic to be at all conclusive and Ewing infers that this writer was misled by the fact that the islands undergo "hypertrophy approaching the structure of the tumor" in these cases.

We shall not dwell extensively upon the history of neuroblastoma, the subject is very well covered in such text-books as Ewing's "Neoplastic Diseases" (1922), and the latest edition of Delafield and Prudden (1922), as revised by F. C. Wood. The papers of Wahl (1914), and Herxheimer (1914), and of Lehman (1917), bring the subject almost up to date and give extensive bibliographies. Since then comparatively few instances of the tumor have been reported. In 1918, Herz and Secher, and Wolbach and Morse (1918) reported cases, in 1919, Comby and Demaria wrote papers on this subject and in 1920, Gunby published a case report and Christin and Naville (1920) described a neuroblastoma metastasizing to the lateral cerebral ventricles.

Neuroblastoma usually originates in, or near the adrenal glands, but it may arise anywhere in the sympathetic nervous system. It may metastasize to the cranial bones, orbit, spine and ribs (Hutchinson's type), or to the liver, (Pepper's type). Metastasis to the musculature of the shoulder (Symmers, 1913), the hilum of the lung (Wright, 1910), or the brain and cerebellum (Christin and Naville, 1920) (Kuroda, Herxheimer, 1914, loc. cit.) is considered so unusual as to render the diagnosis doubtful. The tumor is malignant, only one case of recovery after operative removal is reported; usually extirpation is impossible, owing to the fact that the neoplasm already may be widely disseminated at birth, to the rapidity of metastasis, and to the risks incidental to operations on extremely youthful subjects and in difficult situations. Neuroblastoma occurs almost exclusively in infancy and childhood, Herxheimer (1914), and von Gierke (Aschoff, 1921), maintain that it occurs only during this period of life.

Grossly there is little to distinguish this tumor from lymphosarcoma, though usually it is delimited from the surrounding tissue fairly distinctly, when seen with the naked eye. Histologically, it is characterized by the presence of cells with small, rounded

nuclei which are rich in chromatin and surrounded by an extremely narrow rim of cytoplasm, which tends to fray-out into processes. The elements tend to collect in groups, which may undergo central necrosis, or to gather in rings (Küster's rosettes) about masses of fibrillæ. The latter are very delicate, apt to be granular, do not stain characteristically for glia or collagenous material, and may be demonstrated by ordinary acid stains. They are well shown by Weigert's iron-hematoxylin, followed by Van Gieson's stain, but can be demonstrated to be non-medullated neurofibrillæ only by means of silver impregnations, Bielschowsky or Levaditi. Antischkow, quoted by Lehman (1917), first described hollow rosettes, with their cells arranged about a lumen.

The neuroblastoma is recognized as a product of the proliferation of sympathogonia, or cells intermediate in their developmental stage between primary neurocytes and sympathoblasts, in the non-chromaffin line of descent of the sympathetic system. One tumor, described by Marchand in 1891, was interpreted by him as descending from the primary neurocyte and given the name "neurocytoma." Here there was no fibrillar matrix and the cells were small and rounded, of an extremely primitive type. This is the only true neurocytoma thus far described. Wolbach and Mörse (1918), think that "neuroblastoma" alone and unqualified, is too inclusive and vague a name for this neoplasm, they propose the term "neuroblastoma sympathicum," or "sympathetic neuroblastoma" as an improvement, replacing that of "ganglioma embryonale sympathicum" proposed by Pick. Landau (1912) has stated that the older the patient, the more mature will be the type of cell found in the tumor and the better the chance for recovery, an assumption certainly not borne out by our case, or in the case of other types of malignant new growth.

Case History. J. M., aged thirty-four years, single, waiter, English, admitted July 21, 1922.

Complaint. Knife-like pain in the back of the head.

Family History. Negative.

Past History. No operations nor serious illnesses; has had frequent attacks of hay-fever. There have been no headaches previous to the present illness. The left eye has had poor vision since birth. No otitis media nor tinnitus. Has had very poor teeth, a number of which have been removed. No cardio-respiratory diseases. Appetite has always been good, no nausea nor vomiting. About four years ago the patient had attacks of colicky pain in the epigastrium, which sometimes came twice-a-day over a period of five months. During the attacks the patient became dizzy and fell, but did not lose consciousness. No blood in the stools, diarrhea, nor urinary symptoms. He has always slept well and has not been "nervous." Best previous weight 112 pounds, present weight 110 pounds.

Present Illness. Previous to three weeks ago the patient had been as well as usual and had no complaints. His illness began with headaches of a knife-like character in the back of the head. At first these were slight and did not cause much discomfort, they have increased in intensity and duration until he is now in constant pain which is aggravated at times, becoming unbearable. The headache comes on at any time, bears no relation to exertion, position, or the taking of food. It radiates down the back of the neck, causing some stiffness and retraction, nothing relieves the condition. Two weeks ago the patient felt hot and feverish and began to vomit. He has vomited at intervals since then, the attacks bearing no relation to meals. He was able to work until two weeks ago. The day of admission he fainted on the street and was brought at once to the hospital. Soon after the onset of headache, the patient seemed to have some stoppage of the nose, not being able to breathe freely, but there has been no epistaxis nor nasal discharge. There have been no mental symptoms.

Examination. Temperature, 98.6° F.; pulse, 90; respiration, 16; white blood cells, 11,800; hemoglobin, 90 per cent; red blood cells, 5,000,000. Differential count: Neutrophiles, 80 per cent; small lymphocytes, 4 per cent; large lymphocytes, 14 per cent; eosinophiles, 2 per cent.

The patient is a rather poorly-nourished white man complaining of intense pain in the back of the head, at times convulsed with pain, screaming loudly. He is rational and oriented. Head: There is no "cracked-pot" sound; slight tenderness to percussion to the suboccipital region. No exostoses. A general physical examination is negative with the exception of the following: (1) Pannus over the left eye; (2) deflected nasal septum, (3) marked pyorrhea alveolaris.

Neurological Examination. Cranial Nerves. (I) Sense of smell absent on both sides.

II. No hemianopsia, the right disk is slightly edematous, especially on its nasal half, its vessels are markedly enlarged, no hemorrhages.

III, IV and VI. There is nystagmus, which is most marked toward the right, the pupils are equal and react to light and accommodation. There is partial ptosis of the left lid, no strabismus.

V. Negative.

VII. The left half of the face is flattened, the mouth cannot be drawn as far to the left as to the right.

VIII. No tinnitus, the hearing is equal and good in each ear. No involvement of this nerve can be determined.

IX and X. Negative.

XI. Negative.

XII. Negative.

There is no aphasia. The patient is well-oriented and answers questions well, his memory is good.

There is no motor nor sensory disturbance of the extremities or trunk.

Reflexes. The right knee-jerk is more active than the left, both being hyperactive. There is a poorly-sustained ankle clonus, more marked on the right. The biceps and triceps are hyperactive, more so on the right. The Babinski and Oppenheim on the right are mildly positive.

Cerebellum. (1) Nystagmus to the right; (2) suboccipital pain radiating to the neck; (3) gait slightly ataxic, the patient tends to veer to the left; (4) Romberg is positive, patient falling toward the right; (5) past pointing with both hands, more marked on the right.

Roentgen-ray of the skull showed no abnormality, plates directed toward the accessory sinuses were likewise negative. Blood and spinal fluid Wassermann examinations both negative. The urine shows 0.625 per cent sugar, blood sugar after twelve hours fast (patient on ward diet the previous day) 0.134 per cent. Urine of previous twenty-four hours contained 6.25 gm. glucose per liter. Glucose tolerance on the following day showed: Fasting (twelve hour), blood sugar 0.0932 per cent. The patient was then given 1.7 gm. glucose per kilo of body weight, blood taken at intervals of twenty minutes gave the following sugar estimations: twenty minutes, 0.0935 per cent glucose; forty minutes, 0.15 per cent sixty minutes, 0.12 per cent. The urine examined during and following this test showed no glucose.

The patient was kept under observation for a week, during which he complained constantly of headache, screaming at intervals with the pain. The edema of the disks became more marked, the patient became dull, and drowsy and vomited several times. His temperature did not exceed 98.6° F. His pulse rose to 100, but on the day before operation it fell to 54. The respirations remained regular and from 16 to 20 per minute.

A diagnosis of right cerebellar lesion, most probably an abscess (judging from the rapid onset) was made. The patient was transferred to the surgical service and operated upon July 28, one week after admission.

Operation. A cross-bow incision was made and the cerebellar lobes exposed. A ventricular puncture was done before opening the dura and a great deal of fluid under pressure removed. The dura over the left lobe was opened first, the cerebellum beneath it looked normal. Upon opening the dura over the right lobe, many rather dense adhesions were found near the right cerebellar-pontine angle. The surface of the right cerebellar lobe was yellowish in color, the convolutions widened. On palpation a softened area

was felt in the right lobe, about 6 cm. from the midline, a needle was inserted into it and a yellowish, puriform material obtained on suction. The remainder of the operative field was walled-off with wet cotton, the needle withdrawn and the cerebellum opened along the needle-tract. A cavity containing about 8 cc of puriform, thick material was exposed, two soft rubber tubes were inserted into its depths and a rubber tissue drain down to the angle. A stab-wound was made in the skin and the drains brought directly through to the exterior. The wound was closed throughout with catgut. An adhesive-plaster dressing with a check-rein was applied to prevent flexion of the head.

The patient stood the operation well and was returned to the ward in good condition. The wound healed *per primam*, all drainage being removed within two weeks. At the end of three weeks he was out of bed in a wheel-chair. The headaches had disappeared entirely, he was bright and rational, the nystagmus had disappeared. The decompression was full at first, but soon became flat and pulsated freely. It seemed as though the patient were well.

One month after operation the patient became quite restless, hard to arouse and irrational. There was profuse perspiration, the temperature rose to 103° F., the pulse to 140. At this time the only positive neurological findings were weakness of the left face, generalized spasticity, and a fine tremor of the body and extremities. The decompression was not tight nor bulging and could be seen to pulsate freely. A ventricular puncture revealed about 60 cc of clear fluid under increased pressure and with a normal cell count. A blood count showed 19,000 leukocytes. Daily spinal and ventricular punctures were done, there was no increase in pressure or cells at any time. The spasm and rigidity disappeared, only to return again in an aggravated form just before the patient's death, which occurred on September 21, almost two months after the operation. During the last three weeks of the patient's life he had long periods of consciousness, but was drowsy and hard to arouse. His temperature remained normal until two days before his death, when it rose to 101° F., and remained there until the end. The wound remained well-healed, the decompression pulsated at all times.

The patient's signs and symptoms throughout his convalescence from the operation, did not suggest increased intracranial pressure. This was borne out by the low spinal fluid and intracranial pressure readings with a manometer. There was no evidence of infection of the wound, or of the spinal fluid. The cause of death could not be explained satisfactorily, there was no clinical evidence to account for the postmortem findings in the brain. The large tumor mass in the left frontal region gave no evidence of its position save possibly mental dulling.

Condensed Necropsy Protocol. Necropsy performed twenty-four hours postmortem so that the staff could be present.

The body is that of a well-built, well-developed, but poorly-nourished white male, apparently about thirty years of age. Rigor mortis is complete in extremities and lower jaw. Postmortem lividity is marked in dependant portions and in finger tips. A pannus over the left eye and the operative scar in the suboccipital region are the only gross abnormalities noted on superficial examination.

The heart is acutely dilated and shows a grayish thickening of the epicardium over the left auricular appendage.

The right lung weighs 650 gm. and lies almost free in the pleural cavity, some fibrous adhesions presenting along the convexity in the mid-axillary line and between the lobes. The upper and middle lobes are mottled deep-red on pinkish-gray, they are crepitant in front, but only slightly so behind. Their consistence is increased in the less crepitant portions. The lower lobe is much increased in consistence, but still crepitates. It is of a uniformly deep-red color. On section, the apex of the upper lobe is found to be semi-consolidated, the blood and fluid content much increased while the air content is decidedly diminished. Sections float low in water. Sections from the other lobes are better aerated but much congested and edematous. At the hilum of the organ there is a firm, grayish-white mass of tissue measuring 3.5 x 6 x 4 cm. in size and made up of confluent lobules suggesting lymphoid tissue which has been invaded by a tumor. A milky fluid can be scraped off readily with the knife. The mass infiltrates the tissue about the hilum and bronchial tree and invades the lung in its immediate neighborhood. The left lung and organs of the neck present nothing worthy of mention.

The spleen and liver are not grossly remarkable, the latter is small, pale, brownish-yellow in color and its cut surface shows a delicate nutmeg pattern. The parenchyma is not greasy. The gastro-intestinal tract is not remarkable. In that portion of the mesentery attached to the jejunum is an enlarged lymph node, soft, whitish-gray in color and about 1 cm. in diameter, resembling the mass at the hilum of the lung in every particular.

The pancreas is stony-hard, the head composed of two distinct lobules, and very thick in proportion to the rest of the organ, and measures 7 x 5 x 4 cm. in size. On section, it is found to be composed of more or less homogeneous grayish tissue (resembling the tumor in the pulmonary hilum) which has replaced the pancreatic tissue almost completely. The body of the organ consists of very much fibrosed pancreatic tissue and extends 8 cm. beyond the tumor.

The suprarenals on both sides are firm and spread out over the

surface of the upper pole of either kidney, measuring 5 x 4 cm. in area and but 5 mm. in thickness. Section of these organs reveals a small, globular, milky mass in the right medulla, about 4 mm. in diameter. (This is subsequently ascertained to be normal medullary tissue.) Otherwise they are very poor in medullary substance, being composed chiefly of yellowish cortical tissue which is so intimately blended with the kidney cortex that the organs cannot be separated one from the other.

The kidneys and genito-urinary tract are not grossly remarkable.

The brain weighs approximately 1300 gm. The dura and leptomeninges are in no way remarkable, there is no thickening nor any sign of meningeal inflammation. The left frontal lobe presents a softer consistence than the right, the cerebellar hemispheres are reduced in size, the right by one-half, the left by one-third. They present a scooped-out appearance over their lower aspect, covered with grumous, puriform material and fresh looking granulations, which adhere to the margins of the operative wound. Upon opening the cerebral ventricles the right is found to contain clear, colorless fluid free from turbidity; from the left, however, there gushes a mass of thick, bloody, puriform material. The fact that this comes from the ventricle in a sudden spurt indicates that it may have been expressed from a cavity in the frontal lobe by manipulation. Cross sections of the brain reveal such a cavity, 4 x 5 x 4 cm. in size, situated in the left frontal lobe just in front of the basal ganglia and communicating with the anterior horn of the left ventricle by a ragged opening. The walls of the cavity are ragged and covered with bloody, puriform material. Sections of the left basal ganglia show them to be invaded by the necrotic focus just described, the remainder of the organ is not remarkable. The choroid plexus is noticeably thickened, grayish and nodular, and edematous.

Microscopical Appearance of the Tumor and Organs. The outstanding feature of the microscopical examination is the character and distribution of the tumor; it is found to be composed of small, slightly elongated, elliptical or ovoid cells, with elliptical nuclei rather rich in chromatin, and with a very narrow zone of ragged cytoplasm. They are usually loosely arranged, sometimes appearing to anastomose with one another and sometimes lying free. They vary in size from 10 by 14 microns to 10 by almost 20, in which case they are fusiform. There are three types of arrangement of these cells: (a) In the pancreas (Fig. 1) and lung (Fig. 2) they tend to lie in alveoli, in the former prominently outlined by stroma, in the latter less strongly indicated; (b) in the lymph nodes (Fig. 3) they are very loosely arranged and the alveolar septa scarcely

exist as such, the tumor rather closely resembling a lymphosarcoma; (c) in the choroid plexus they are closely packed (Fig. 4), more cylindrical than elsewhere and are arranged more or less at right angles to the choroid vessels, forming palisades along their adventitia. In their looser arrangement they tend to form balls (Fig. 2), which are often necrotic at the center; or to group themselves about a central axis resembling a lumen, like hollow rosettes (Fig. 3). There is an extremely delicate and granular matrix about the loosely arranged cells, which resembles either cytoplasmic debris or broken-down fibrillæ. Sometimes this material can be seen to form short, curling threads, which stain pink with eosin,

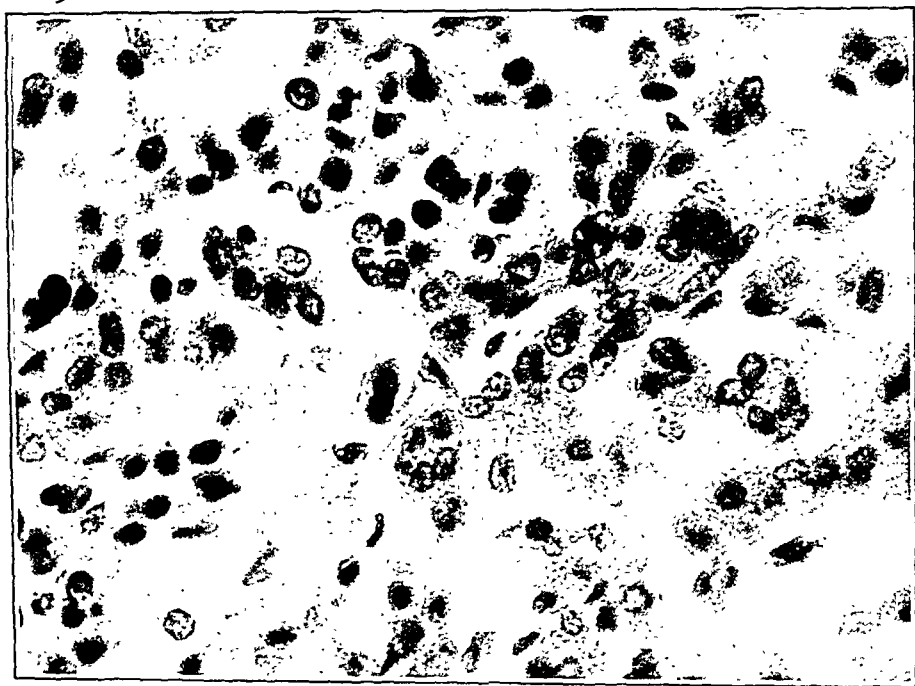


FIG. 1.—The tumor in the pancreas; no sharp distinction between tumor tissue and pancreatic structure. $\times 800$. Hematoxylin-eosin.

purplish with phosphotungstic acid hematoxylin, and faintly grayish-pink with Van Gieson's stain. No Bielschowsky preparations were made.

Tumor cells are found in sections from the brain, cerebellum, choroid plexus, hilic nodes of the lung, lung tissue, pancreas, mesenteric nodes and nodes in the omentum. In the heart tiny metastatic emboli of tumor tissue, measuring from 80 to 100 microns in long diameter, are present in the capillaries.

In the lung the tumor has invaded the alveolar walls, air-sacs and lymphatics about the hilum. The spleen is free from tumor cells. The liver shows central necrosis and congestion of the

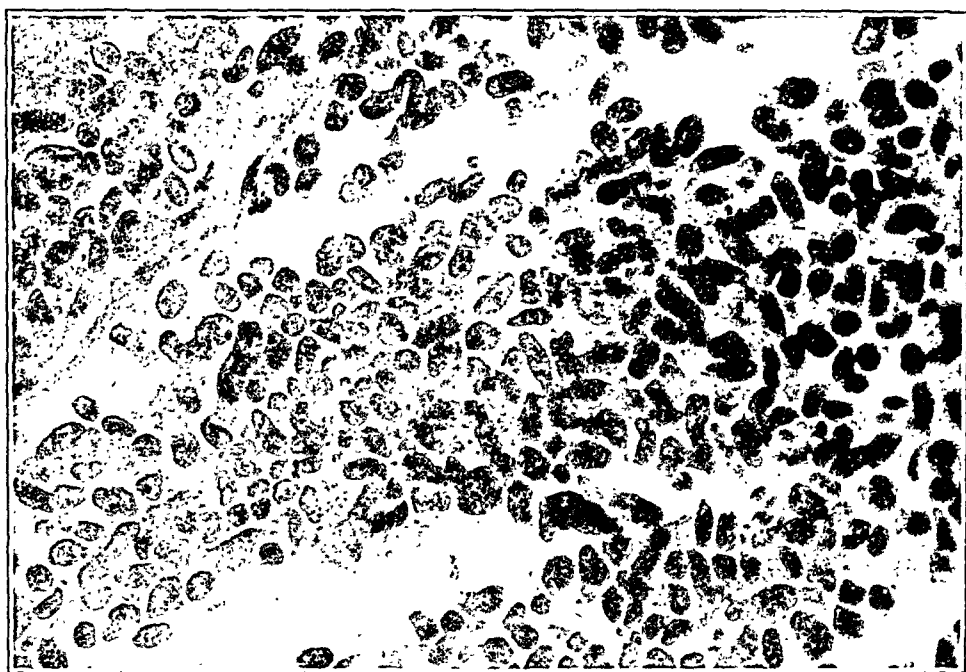


FIG. 2.—Mass of tumor tissue in hilus of lung; two mitotic figures near center. $\times 800$. Hematoxylin-eosin.

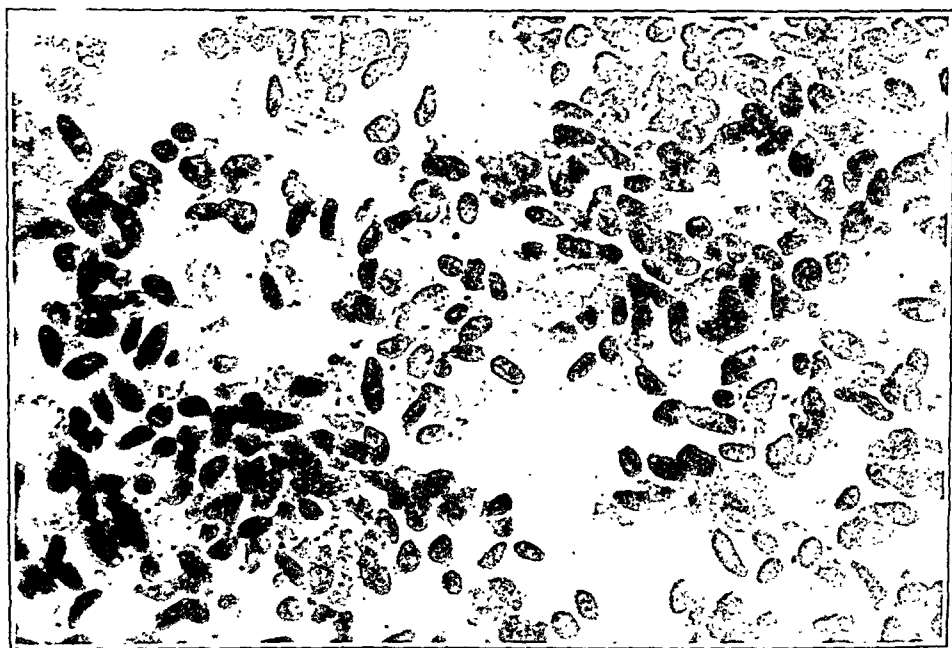


FIG. 3.—The tumor in a mesenteric lymph node; note the tendency to form clumps and hollow rosettes. $\times 800$. Hematoxylin-eosin.

chronic passive type, but no tumor metastases are found. Large, "water-blister," vesicular nuclei suggest glycogenic infiltration; the nuclear membrane is wavy and indented, the nucleus several times larger than normal, its chromatin practically gone.

The pancreas shows extensive involvement by the tumor and sections from the head show but little pancreatic tissue, only a few ducts being left. The body of the organ, where not infiltrated by the tumor, has undergone extensive atrophy and fibrosis and the acini have been destroyed. The islands of Langerhans have been destroyed also, but those that survive are well-formed and perhaps a trifle larger than usual. The tumor follows the course

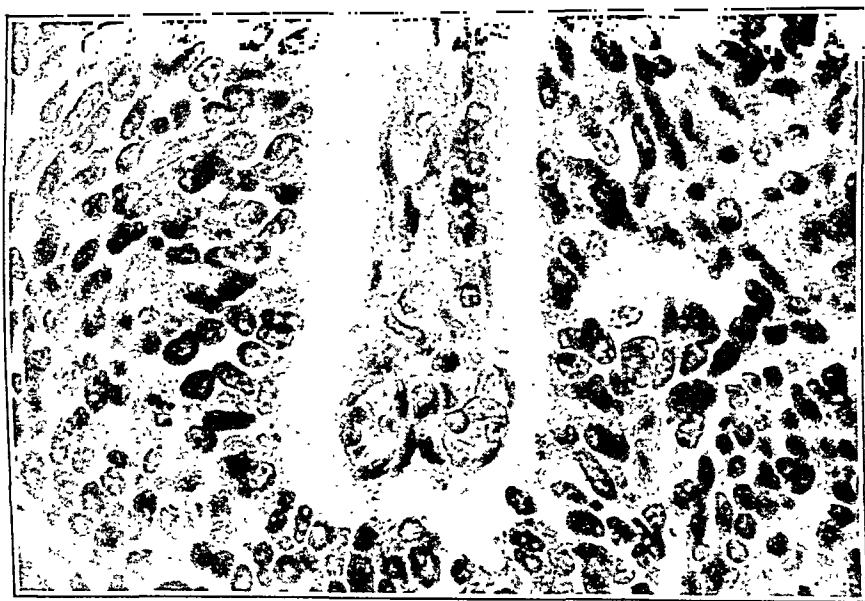


FIG. 4.—Palisade arrangement of tumor cells about a vessel in the choroid plexus, epithelial type of growth. $\times 800$. Hematoxylin-eosin.

of the larger ducts in its distribution. There are occasional situations where one can find an apparent merging of tumor cells into frankly epithelial cells resembling the parenchymatous elements of the organ. (Fig. 1.) This might be interpreted in two ways: The transition of non-neoplastic into neoplastic tissue, or the wearing-down or pressure atrophy of the parenchymatous cells by the invading tumor. If the latter be true, we might expect a more distinct line of demarcation between the two.

Sections from the kidneys and adrenals, where they adhere, show a remarkable interlacing of the kidney cortex with adrenal cortex (Fig. 5), the capsule of the kidney being interrupted, or wanting, over comparatively large areas and its cortical cells growing into the adrenal cortex, or *vice versa*. Otherwise the renal tissue is not remarkable.

Sections from the choroid plexus show massive invasion by the tumor, which in these preparations shows a more solid type of growth, as already described. The cerebral tissue and sections from the margin of the cerebellar "abscess," show extensive necrosis and destruction by the tumor, without much tumor tissue surviving. It seems as though the latter had undergone almost complete dissolution in these organs, the necrotic tissue escaping at necropsy and being lost, leaving only the more healthy remnants at the periphery of the growth behind.

We are much indebted to Dr. Ewing for pointing out the resemblance of this growth to that described in his article, already

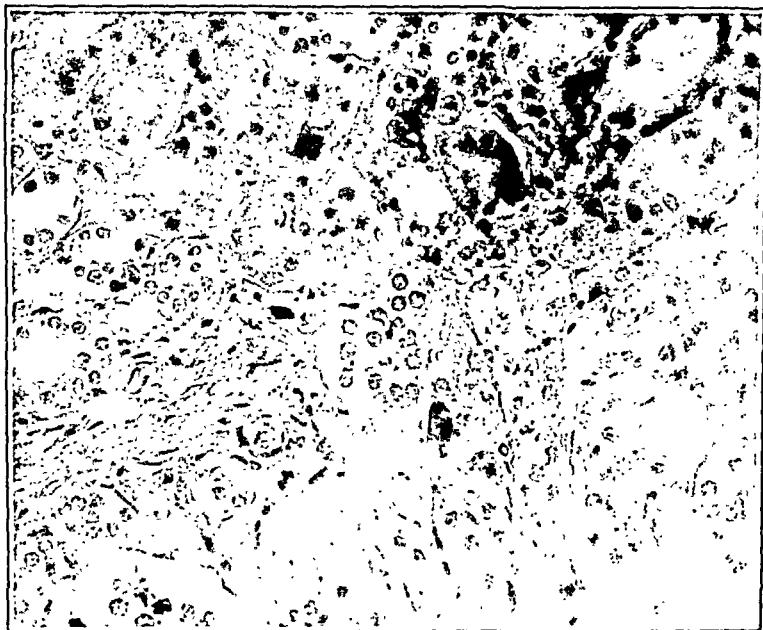


FIG. 5.—Blending of adrenal, with renal cortex; the kidney capsule runs diagonally part way through the field. $\times 400$. Hematoxylin-eosin.

referred to. He stresses the typical carcinomatous appearance of the choroid metastasis and the vague intermingling of tumor cells and acinar cells of the pancreas in making his diagnosis of anaplastic carcinoma of the pancreas. He also calls attention to the advanced fibrosis in the pancreas as typical of carcinoma, often preceding its appearance and, he thinks, leading to it. For a diagnosis of neuroblastoma he insists upon the presence of the typical rosettes arranged about definite neurofibrillæ, both of which are wanting in this tumor. (Personal correspondence, J. E. and N. C. F.)

Discussion. From a medical point of view it is interesting to consider, in retrospect, the cause of the glycosuria. Sugar was

discovered in routine examination of the urine; there were no symptoms of diabetes, such as polydypsia, polyuria, or recent loss of weight. Blood sugar values were within the normal range. Aside from the presence of sugar, the urine was normal, no acetone and no diacetic acid were present, nor was albumin. Sugar tolerance was approximately normal during the first hour. There are two possibilities in view of the postmortem findings, which might have been responsible for the glycosuria. The pancreatic tumor with its attendant destruction of glandular tissue could have produced a lowered sugar tolerance. This is not supported by the sugar tolerance test which showed no hyperglycemia in this case, and a normal ability to handle carbohydrates. It is more probable that the increased intracranial pressure was associated with stasis of the cerebrospinal fluid, producing glycosuria similar to that mentioned by Cushing (1912), Osler (1919), and others. In this connection it may be mentioned that no glycosuria was present after the relief of intracranial pressure by decompression.

From the pathological standpoint we are chiefly interested in the true nature of the tumor. Was this a carcinoma or a neuroblastoma? Before considering the points in favor of and against one or the other diagnosis, there are several features in the pathology of this case that should be recapitulated. In the first place, the patient was much too old for neuroblastoma sympathicum, judged by the usual standards; he was also somewhat young for carcinoma. Although he must have had these tumors for some time, it was not until the cerebellar metastasis had reached a certain stage that he had any symptoms referable to neoplasia, unless one regard his attacks of colicky pain and vertigo (mentioned in the past history) as such. The very extensive necrosis of the cerebral and cerebellar metastases is sharply contrasted with the excellent preservation of the tumor in the choroid plexus and pancreas; this may have been due largely to the fact of the autopsy being done twenty-four hours postmortem, but the preservation of other tissues, usually quite susceptible to such decomposition, was good and the tumor as observed during the decompression and evacuation of the cerebellar "abscess" already presented a puriform appearance.

Let us consider, in closing, the points for and against the two types of tumor already mentioned. In favor of carcinoma we have (a) The primary site (?) in the head of the pancreas; (b) metastases to the lung are more common in carcinoma than in neuroblastoma; (c) the type of cells in the choroid metastasis is definitely epithelial, with a palisade arrangement; (d) there is an alveolar arrangement in the pancreas and, to a lesser degree, in the lung; (e) no neurofibrillæ or Küster's rosettes are present; (f) The tumor fades into quasi-normal pancreatic tissue, without a sharp line of demarcation.

Against carcinoma we have the facts that: (a) Metastases in the liver are wanting; (b) the cells are very atypical in the lymph node metastases and parts of the lung; (c) no definite alveolar arrangement can be found in many situations; (d) the patient is comparatively young.

For a diagnosis of neuroblastoma sympathicum we find: (a) The primary site is near the embryonal origin of the suprarenals; (b) a developmental anomaly of the suprarenals is present; (c) the type cell compares rather closely with the sympathogonium in many instances; (d) there is a loose, anastomosing arrangement of the cells; (e) the granular matrix in which these cells often lie may represent degenerated neurofibrillæ; (f) hollow rosettes resembling those of Antischkow are present.

Against neuroblastoma we may set the following items: (a) Atypical sites of metastasis; (b) the absence of Küster's rosettes and of definite neurofibrillæ; (c) the epithelial type of growth in the choroid plexus; (d) the patient is older than is usual in this type of tumor.

Conclusion. The reader must be left to judge for himself on the strength of the evidence submitted, although, now that the resemblance has been called to our attention, we feel that the tumor represents a very metaplastic type of carcinoma, rather than a neuroblastoma. There is nothing to substantiate a diagnosis of sarcoma: The presence of stroma and of an attempt at lumen formation both point to epiblastic, rather than to mesoblastic origin. In closing, it might be well once more to call attention to the superficial resemblance of such tumors to sarcomata and to advise a close scrutiny of any new growths in the pancreas which might suggest such a diagnosis, before pronouncing them to be sarcomata.

REFERENCES.

Aschoff, L.: *Pathologische Anatomie*, Gustav Fischer, 1921, 5th ed., 1, 763; 2, 1002.

Christin and Naville: *Schweiz. Arch. f. Neurol. u. Psychiat.*, 1920, 7, 49.

Comby, J.: *Arch. de méd. d. enf.*, 1919, 22, 142; abstract, *Jour. Am. Med. Assn.*, 1919, 72, 1332.

Cushing, H.: *The Pituitary Body and Its Disorders*, J. B. Lippincott, Philadelphia and London, 1912, pp. 172, 262.

Delafield and Prudden (Ed.—F. C. Wood): *Text-book of Pathology*, Wm. Wood, New York, 1922, 12th ed., p. 408.

Demaria, E. B.: *Semana méd.*, 1919, 26, 173.

Ewing, J.: *Neoplastic Diseases*, W. B. Saunders, Philadelphia and London, 1922, 2d ed., pp. 405, 705, 772.

Fabozzi, S.: *Beitr. z. path. Anat. u. z. allg. Path.*, 1903, 34, 199.

Fowler, R. H.: *Med. Rec.*, 1920, 98, 767.

Goldstein, H. I.: *Am. Jour. Surg.*, 1922, 36, 23.

Gunby, P. C.: *AM. JOUR. MED. SCI.*, 1920, 160, 207.

Hertz, P., and Secher, K.: *Hospitalstid.*, 1918, 60, 278; abstract, *Jour. Am. Med. Assn.*, 1918, 70, 278.

Herxheimer, G.: *Beitr. z. path. Anat. u. z. allg. Path.*, 1914, 57, 112.

- Horgan, E. J.: Jour. Lab. and Clin. Med., 1920, 5, 429.
 Lehman, E. P.: Jour. Med. Research, 1917, 31, 309.
 Lockwood, C. D.: Jour. Am. Med. Assn., 1921, 77, 1554.
 Marchand, F.: Festschrift f. Rindfleisch, Leipzig, 1907.
 Osler, W.: The Principles and Practice of Medicine, Appleton, 1919, 8th ed., pp. 427-428.
 Speed, K.: AM. JOUR. MED. SCI., 1920, 160, 1.
 Symmers, D.: Jour. Am. Med. Assn., 1913, 60, 337.
 Wahl, H. R.: Jour. Med. Research, 1914, 25, 205.
 Wolbach, S. B., and Morse, J. L.: Am. Jour. Dis. Child., 1918, 16, 63.
 Wolbach, S. B., and Tileston, W.: AM. JOUR. MED. SCI., 1908, 135, 871.
 Wright, J. H.: Jour. Exper. Med., 1910, 12, 556.

TORULA INFECTION IN MAN.

By W. M. SHEPPE, M.D.,

LABORATORY OF BACTERIOLOGY AND PATHOLOGY, UNIVERSITY OF VIRGINIA,
 UNIVERSITY, VIRGINIA.

Introduction. In a recent report Marshall, Sheppe and Glass¹ record the occurrence of a clinically obscure pulmonary infection which was diagnosed at autopsy as an organizing bronchopneumonia. Routine study of frozen sections of lung tissue revealed the presence of numerous yeast-like bodies which were later recovered in pure culture.

It will be the purpose of this paper to: (1) Record in detail the characteristics of this rather unusual virus; (2) to describe the morbid anatomy and types of disease produced; and (3) to propose a more definite and exact nomenclature for the fungus infections based on their botanical relationships.

ABSTRACT OF CASE HISTORY. Med. No. 9512; University of Virginia Hospital.

On November 11, 1921, R. A., a native of Virginia, was admitted to the hospital complaining of "stomach trouble" and "rheumatism."

The patient was a white man, aged about fifty years; a farmer by occupation. He did not appear to be seriously ill.

History. The family history was unimportant and the past history was negative except for frequently recurring gastric upsets accompanied by joint and muscular pains.

Present Illness. The patient dated the onset of his present illness four months before his admission to the hospital. At that time he developed a very severe and persistent tonsillitis with pain and stiffness of the neck. There was considerable loss of weight during this period.

Physical Examination. The patient was somewhat anemic in appearance. The tonsils were congested but not enlarged. Lungs

and heart negative. Passive motion of the joints produced pain but there was no other evidence of an arthritis. Nervous system, negative.

Blood-pressure: 135-100. Temperature: 100° F.

Laboratory Findings. Blood: Hemoglobin, 89 per cent; red count, 5,100,000; leukocytes, 8000. Differential count: Polymorphonuclears, 65 per cent; small mononuclears, 30 per cent; large mononuclears, .3 per cent; eosinophiles, 1.5 per cent; basophiles, 0 per cent; transitionals, 0.5 per cent. Wassermann, negative. Urine: Specific gravity, 1020; reaction, acid; sugar, negative; albumin, 2 mm. ring; 8 to 12 pus cells per high-power field; few red blood cells and a few hyaline and granular casts. Kidney functional test, 65 per cent (phenolphthalein). Smears and cultures from throat, negative. Gastric analysis, negative. Sputum, negative for *Bacillus tuberculosis*. Roentgenogram of chest, negative.

Course of the Disease. The patient improved symptomatically until November 23 (twelve days after admission), when he suddenly became very ill, the temperature rising to 104° F. Four days later moist and crepitant rales, together with a pleural rub were heard on the right side. Signs of consolidation of the entire right lung were noted. During the first week in December the right chest continued dull and the left base became dull. Aspiration of the chest resulted in a dry tap. Repeated examination of the sputum failed to disclose the presence of *Bacillus tuberculosis*. The leukocytes were never over 8000. The patient gradually became worse and died, January 16, 1922, almost two months after the onset of his acute illness.

Diagnosis at the Time of Death. Unresolved pneumonia.

Necropsy (only positive findings recorded): *External Appearance.* Emaciation; skin pale and dry; a few small scars, infiltrated with brown pigment scattered over the chest.

Abdominal Cavity. Dense, fibrous adhesions in regions of gallbladder and spleen.

Liver. Pale, slightly hazy yellowish appearance, suggesting early regressive changes of a fatty nature.

Spleen. Soft; no detail on section; pulp could be scraped away on knife.

Kidneys. Bands of fibrous tissue extended between the pyramids; hazy appearance of cut surface; thinning of cortex.

Thoracic Cavity. Pericardium adherent to pleura on left side; many old, dense, fibrous adhesions covering surface of left lung and to some extent that of right lung; fresh adhesions intermingled with old adhesions; bases of both lungs adherent to diaphragm; no free fluid in either pleural cavity; marked anthracosis of both lungs.

Left Lung. Lung crepitant and apparently normal on palpation; marked congestion noted on section; two small calcified tubercles in superior lobe.

Right Lung. Gross appearance: Lower lobe of lung moderately firm on palpation. The consolidation is not as definite as that noted in ordinary lobar pneumonias at the stage of gray hepatization. Neither the visceral or parietal pleuræ are involved. On section the tissue offers a distinct resistance to the stroke of the knife. The cut surface is relatively dry but is covered by a glairy, gelatinous substance which is scraped away with difficulty. Underneath this mucoid material the lung tissue is dark brown in color. Close examination shows the involved area to be divided into irregular nodules. The outline of these nodules can be made out only by careful inspection. On palpation they feel slightly denser than the surrounding tissue. The outline in some instances fades imperceptibly into the surrounding congested area. There is no apparent relationship to the bronchi in the distribution of the nodules. Plugs of a brownish material resembling antemortem clot may be expressed from the bronchioles, but the larger bronchi are clear. Thin laminae of young fibrous tissue traverse the lung in all directions. Between the nodular areas the alveoli are congested but still crepitant. Microscopical appearance: The epithelium of the bronchi shows marked regressive changes and here and there has completely disappeared. The peribronchial tissue is infiltrated with small mononuclears. The lumina contain zoöglea-like masses of yeast cells firmly bound together by their gelatinous capsules and retracted from the periphery of the bronchi. Intermingled with the cellular masses are many desquamated cells from the bronchial mucosa and a few erythrocytes. The walls of the alveoli are thickened by the proliferation of the fibrous tissue. The lumina contain desquamated alveolar epithelium, many erythrocytes, small mononuclear leukocytes and a few yeast cells. Scattered irregularly through the field are occasional plasma cells and giant cells. A few lymphocytes are seen which have ingested small yeast cells. The giant cells seem to confine themselves to the removal of cellular debris. There is no evidence of a fibrin deposit. Many small strands of young fibrous tissue are entwined among the alveoli. The distribution of this connective tissue leads to the assumption that it represents a process of repair rather than of defense. The edge of the advancing infection is marked by a rather dense plasma cell and small lymphocyte infiltration, but there is no evidence of a fibrous tissue proliferation at this point. The pleura is not thickened.

Anatomical Diagnosis. Organizing bronchopneumonia; congestion of both lungs; fatty degeneration of the liver; acute splenic tumor; chronic interstitial nephritis; chronic fibrous pleurisy,

bilateral; anthracosis, bilateral perisplenic adhesions; adhesions around gall-bladder; depressed scars over chest wall; emaciation.

DISCUSSION OF THE CASE. The patient entered the hospital complaining of indefinite symptoms and giving a history which was unrelated to subsequent events. While under observations an acute pulmonary condition suddenly developed. Despite the very low white cell count the diagnosis of lobar pneumonia was made on the clinical findings. The lung involvement persisted. After the lapse of five weeks there was little change in the general condition of the patient. Tuberculosis, lung abscess and syphilis of the lung were all considered as possibilities. A provisional diagnosis of unresolved pneumonia was made shortly before death. Laboratory procedures were of little assistance in reaching a diagnosis. In fact, the persistently low leukocyte count was a confusing factor throughout. There was no evidence of involvement of the central nervous system. At autopsy the right lung showed evidence of a subacute infectious process, the morbid anatomy of which was unfamiliar to the author. This was accompanied by the usual systemic evidences of an acute infection of considerable duration.

ISOLATION OF ORGANISM. The observance in frozen sections of small round bodies clustered within and without the bronchi and scattered along the alveolar walls led to the belief that some form of yeast was, perhaps, the causative factor of the disease. With this as a clue, work leading to the recovery and identification of the organism was begun. Procedure: The lung was opened with a scalpel and one of the slightly circumscribed nodules dissected out. This was placed in sterile salt solution and cut into small pieces. A single piece was selected and passed through five washings of sterile salt solution, the final washing ending in maceration of the tissue. With this suspension of finely divided lung tissue, the following culture media were inoculated: Glucose agar plates, pH 7; deep tubes of glucose agar, pH 7; deep tubes of glucose broth, pH 7; incubation at 37° C. and 23° C. for thirty-six hours.

In this time numerous colonies developed on the plates, all of which however proved to be Gram-positive cocci. Twenty-four hours later smears from the original saline suspension showed the presence of many yeast forms. The following media were then inoculated from the suspension: Lactic acid agar, lactic-acid-potato agar, lactic-acid-bread agar, bread agar, potato agar (stroke plates in each instance). Incubation: Thirty-six hours at 37° C. and 23° C.

At the end of the period of incubation numerous yellowish-white colonies with raised centers appeared on all the media. These colonies were found to be composed of the same yeast-like bodies noted in the suspension. A certain percentage of the colonies showed small round black "caps" lying a little to one side

of the apex. The organisms obtained from these black-capped colonies were identical with those from other colonies and when transferred produced the ordinary yellowish type of colony. This "capping" did not recur in an extensive series of subcultures.

At the same time that the above inoculations were made a rabbit was inoculated in the following manner: The original saline was centrifuged at high speed for fifteen minutes. The supernatant fluid was poured off and replaced with sterile salt solution. With the purpose in view of inhibiting the growth of contaminating bacteria the suspension was heated to 55° C. for twenty minutes. A rabbit's trachea was exposed under ether anesthesia and 3 cc of the heated suspension injected into the trachea and bronchi. The rabbit was sacrificed at the end of three weeks. The morbid anatomy of the lung was similar to that described above in the human lung. The organism was recovered in pure culture.

Subsequent attempts to reproduce the disease in rabbits by intratracheal inoculation were unsuccessful.

Numerous pure subcultures were obtained from the lactic acid agar plates.

It will be noted from the above that:

1. The organism was obtained and grown in pure culture from the original lesion.
2. The disease was reproduced by animal inoculation.
3. Was recovered in pure culture from the experimental lesion.

DESCRIPTION OF ORGANISM. *Morphology.* The size of the cells varied from 2 to 13 microns in diameter. The larger organisms were surrounded by a densely staining double cell wall about 0.5 micron in thickness. This in turn was enveloped by a transparent, slightly refractile membrane or capsule. This capsule was apparently gelatinous or mucoid in nature as the organisms frequently clumped together in zoöglea-like masses which were not broken up by the ordinary technic of making smears. Further evidence of the gelatinous nature of the capsule was given by the fact that in cultures contaminated by bacilli, the bacilli were caught and held along the periphery of the capsule, and in some instances formed a complete ring around the yeast cell. The smaller organisms were not surrounded by the cell wall or if it was present it was very thin. The general appearance of the cells varied, depending on the freshness of the culture and the nature of the environment. Old cultures (more than four weeks old) showed the granular substance pushed to one side and the main body of the cell occupied by a large clear, faintly staining vacuole. This vacuole often contained dark staining granules varying in size. In the younger cells almost the entire cell was composed of dark staining, granular material. This chromatic substance was not surrounded by a nuclear membrane and it was often distrib-

uted irregularly in the cytoplasm. Whether or not it represents the true nucleus of the cell is a matter at present in dispute.

In some cells the granular material was seen in rapid Brownian movement. This was best observed in hanging drops made in dilute methylene blue. In such preparations the cells appeared much smaller than in smears, due in all probability to the flattening out of the cell when the smear is made. This fact together with the intracellular Brownian movement and the variable distribution of the granular material suggests at once that the cytoplasm is fluid in nature.

Staining. The organism stained easily with any of the usual stains. Four-day cultures on glucose agar were used in the staining experiments. Methylene blue: Granular material dark blue, cytoplasm varying from light blue to pink. Safranin: Granular material and cytoplasm deep pink. Gentian violet: Overstains very easily; not satisfactory. Carbol fuchsin: Granular material and cytoplasm deep red. Fuchsin (water soluble): Granular material and cytoplasm light pink. Gram stain: Fresh cultures, Gram-positive; old cultures, Gram amphophile. Acid-fast stain: Non-acid fast. Methylene blue proved to be a very effective stain as the light pink or purple of the cytoplasm offers considerable contrast to the deeply staining granular material and cell wall. Wright's stain: No differentiation between unit elements of cell.

Cultural Characteristics. After the organism has become adapted to the artificial environment, it grew with ease on all types of media. Incubator and room temperature were equally favorable. Raw potato and lactic-acid-potato agar produced slightly more rapid and profuse growth than the other media. In common with the other fungi this yeast is capable of growing in a very wide range of pH values. Fairly abundant growth was obtained on plain agar having a pH as low as 3 and as high as 8. This characteristic was of considerable aid in obtaining pure cultures as the usual contaminating bacteria failed to survive such a remarkable degree of acidity or alkalinity. The characteristic colony was circular in outline, yellowish-white in color and with a sharply circumscribed margin. The center was raised, the colony sloping symmetrically in all directions. The size varied from 0.5 to 1 cm. in diameter. The individual organisms were seen with the 1/4 objective as small refractile globules packed closely together.

The colonies, like those of other fungi, were closely adherent to the surface of the medium, requiring a stiff platinum needle for fishing.

On solid media slants the colonies rapidly fused and in the older cultures grew up the sides of the tube. Growth was less abundant in liquid than in solid media. The supernatant fluid was clear and there was no evidence of pellicle formation.

A series of cultures studied over a period of eleven months have failed to show the slightest tendency to mycelial formation.

Physiology and Reproduction. Aërobic, facultative anaërobic. Temperature range, 20° C to 40° C. pH range, pH 3-8. Nitrate production, negative (sulphanilic a-naphthylamine test). Indol production, negative (Dunham's peptone solution—Salkowski-Kitasato reaction). Hemolysis, negative; gelatin was not liquefied. Carbohydrate fermentation: Smith fermentation tubes; positive and negative controls; 1 per cent solutions of carbohydrate in nutrient broth, pH 6. Sucrose, dextrin, inulin, mannit, glucose, levulose, starch, lactose, galactose and glycerine showed no evidence of gas formation at end of five days. Acid formation was noted, the majority of the tubes reaching a pH of 4.6. Litmus milk, faintly acid; no coagulation. Sporulation: Ascus formation, absent; exospores, absent. Cultures placed on gypsum blocks failed to produce spores during an observation period of four weeks. The yeast resisted the unfavorable environment by the formation of chlamydospores. These were rather large cells in which the cell wall had become several times thicker than normal. The cytoplasm was clear and refractile. Following the reestablishment of favorable conditions these resting cells bud very rapidly and profusely.

Gemmation. Reproduction was entirely by budding. The small cells of rapidly growing cultures gave off buds as freely as did older cells, the bud often equalling the parent in size.

Observations made on micro-cultures showed the following series of events:

- (a) A slight protuberance appears on the side of the parent cell.
- (b) This protuberance enlarges and both layers of the cell membrane stretch over the bud.
- (c) Nuclear material passes into the bud.
- (d) The pedicle of the bud is often considerably elongated and at this stage is composed entirely of the two layers of cell membrane. The bud begins to increase in size, the whole presenting a curious "dumb-bell" appearance when it reaches the size of the parent.

(e) After about twenty hours (at room temperature) the process is completed by the constriction and final severance of the pedicle. This severance leaves both organisms pyriform in shape. The rounded contour is gradually reassumed. Gemmation of the larger cells resembles closely the casting off of polar bodies by the maturing ovum. The outline of these larger cells are unchanged in the process.

The following media were used in the study of cultural and morphological characteristics:

Solid Media. Sabouraud's agar, pH 3-8; blood agar; nutrient, pH 3-8; glycerine; lactose; sucrose, pH 7; starch; glucose; 0.3 per

cent lactic acid agar; 0.3 per cent lactic-acid-potato agar; 0.3 per cent lactic-acid-bread agar; Löffler's blood serum; gelatin, pH 7; potato, apple, carrot, cabbage, beet.

Liquid Media. Carrot, potato, apple, prune, cabbage and manure decoctions; nutrient broth, pH 7; glucose broth, pH 6; litmus milk; salt solution, 7.5 per cent; Dunham's peptone solution.

Agglutination. Blood serum withdrawn from rabbits inoculated with the virus; a suspension of yeast cells in salt solution, with dilutions of 1 to 25, 1 to 50 and 1 to 100. Result: Negative in all dilutions.

BACTERIOLOGICAL DIAGNOSIS. The studies detailed above established the fact that we were dealing with a yeast which reproduced by budding, did not form ascospores, did not form mycelia and failed to ferment any of the sugars. On this basis the organism was tentatively placed in the group *Fungi imperfecti*, subgroup *torula*.

Discussion. **INCIDENCE.** The difficulty of obtaining an approximate idea of the frequency of torula infections was at once made manifest when a review of the literature of the pathogenic fungi was begun. The terms used to designate these infections were for the most part vague and applied without regard to the presence or absence of differentiating criteria as adopted in the accepted botanical classifications. This necessitated a careful review of each case cited, whether the causative agent was recorded as torula, yeast, blastomycosis, oïdiomycosis or *Coccidioida granuloma*. The results of this search revealed the fact that only 10 authentic cases of torula infection in man are recorded, the case herewith reported from the University of Virginia brings the total to 11. In 5 other cases mentioned the data given is insufficient for an accurate classification to be made. These cases are included as "doubtful" in the table on page 99.

It is likely that many more torula infections in man have occurred but they are either unrecorded or are so meagrely described that their recognition as such is impossible.

HISTORICAL. About the beginning of the twentieth century much interest was excited in medical circles by the isolation in pure culture of certain small circular "bodies" from various types of neoplasms. These bodies were called "inclusion bodies," "Plimmer's bodies," or "cancer bodies." Weis,² after a careful study of the cultures of Sanfelice, Plimmer and Klein, came to the conclusion that he was dealing with a form of yeast and identified the organism as belonging to the subgroup *torula*. Nichols³ and Greenough⁴ corroborated this finding and, further, decided that the yeast was not the etiological agent of any form of neoplasm. Before this time Busse⁵ and Curtis⁶ had pointed out the pathogenicity of some of the yeasts for man and animals, and numerous reports of yeast infections occurred in the literature from 1896

to 1915. During this period Gilchrist^{7 8} was able to identify a yeast form as the cause of a particular type of dermatitis and called the disease blastomycosis. Certain hitherto obscure systemic infections were found to be due to this yeast, but bacteriologists and mycologists found many puzzling differences in the morphology and physiology of the organisms isolated from different sources. The irregularity in morphology was accepted as an evidence of the extreme variability of this class of organisms. It was not until 1915 that Wolbach⁹ advanced the idea that this supposed variability of one organism was in reality an indication that several different yeasts were being dealt with. This author, however, failed to furnish the differential criteria by which the various types might be separated. Wade and Bel¹⁰ recognized the fact that closely related fungi were capable of producing infections which differed as to distribution, treatment and prognosis. It remained, however, for Stoddard and Cutler¹¹ to furnish the complete data for the differentiation of the pathogenic yeasts and the infections which they respectively produce. This comprehensive monograph apparently escaped general notice, for since the time of its appearance, in 1916, the literature continued to abound in confusion of nomenclature and classification of yeast infections. No further mention of torula infections as a disease entity is made until the appearance in 1922 of a case report by Evans.¹²

TABLE 1.—COLLECTED CASES OF TORULA INFECTION IN MAN
(AUTHENTIC CASES).

Observer.	No. of cases.	Sex.	Age.	Race.	System chiefly involved.	Result.
1. Brewer and Wood	1	M.	20	Russian	Muscles-vertebral column	Recovered.
2. Pierson	1	M.	57	Amer. Cal.	C. N. S.	Fatal.
3. Stoddard and Cutler	1	F.	42	Amer. Fla.	C. N. S.	Fatal.
4. Stoddard and Cutler	1	M.	39	Amer. Mass.	C. N. S.	Fatal.
5. Rusk	1	M.	57	Germ. Cal.	C. N. S.	Fatal.
6. Rusk	1	Germ. Cal.	C. N. S.	Fatal.
7. Turek	1	F.	43	German	C. N. S.	Fatal.
8. v. Hanseemann	1	M.	18	German	C. N. S.	Fatal.
9. Evans	1	M.	13	Mexican Cal	C. N. S.	Fatal.
10. Evans	1	F.	20	Mexican Cal	C. N. S.	Fatal.
11. Sheppe	1	M.	48	Amer. Va.	Pulmonary	Fatal.
DOUBTFUL CASES.						
1. Verity	1	The work of Verity was not available for examination. Cited from Wade and Bel.				
2. Breed	2	These cases are not reported in the literature. Mentioned as having been seen by Wade and Bel. One was pulmonary in type and fatal, the other one recovered.				
3. Confrères of Wade and Bel	2					

ETIOLOGY. *Source.* Torula is well-known to botanists and mycologists, as the genus is found widely distributed in Nature. It has been cultivated from wasp nests, the stems of many plants and grasses, the bodies of numerous insects and pickle brine.^{15 16 17} It seems probable that all types of torulae are originally non-pathogenic in Nature, but under suitable circumstances are capable of producing disease.

Distribution. (a) Geographical: Nine of the 11 cases reported occurred in the United States. Of these 9, 5 were discovered in California (60 per cent), the remaining 4 were scattered over the country from Massachusetts to Florida (see Table I).

(b) Sex: The infection occurs more often in men than in women. The sex of the patient was recorded in 10 cases and of these 7 were men.

(c) Age: The age of the patients varied from thirteen to fifty-seven years, the average age being thirty-six years.

(d) Occupation: The majority of the patients were engaged in manual labor of various kinds. One case of Stoddard and Cutler occurred in a school teacher.

The number of cases investigated is as yet far too small to furnish the basis for any general conclusions based on the preceding statements. An attempt to make reliable deductions from so small a series would be entirely futile.

Mode of Entry. The portal of entry into the body apparently varies considerably, but the consensus of opinion lays emphasis on the respiratory tract. In Türk's¹⁴ case a sticky esophageal exudate was noted, suggesting that the gastro-intestinal tract was the first involved. In several other cases the oldest lesion was in the lungs. This was regarded as the primary focus of the infection. The relatively great number of cases, involving principally the central nervous system, suggests that the organisms may have reached the cranial cavity directly from the upper nasal passages *via* the cribriform plate. No direct evidence can be offered to support this statement. In the case herewith reported, a prolonged and severe tonsillitis was noted. This may or may not have marked the entrance *via* the tonsils. There is no case on record in which the infection entered through the skin.

MORBID ANATOMY. The fact that torula infections occur most frequently in the central nervous system seems to be well established. That this in all cases is due to the direct invasion of the cranial cavity *via* the upper nasal passages is unlikely. If susceptible animals are inoculated intravenously or intraperitoneally typical lesions are usually found in the viscera, but in the brain and meninges these lesions are much more numerous and extensive and not infrequently are the sole macroscopical evidence of infection. The humoral elements of the defensive system are without

doubt equally as active against these infections in the brain as elsewhere in the body, but the cytological changes are confined to a sluggish leukocytic reaction. Thus a local susceptibility of nervous tissue may be said to exist and perhaps account for the frequent involvement of this tissue. The lungs come next to the brain, followed in order of resistance by the spleen, liver and kidneys. In the last three organs the focus of infection is always small and circumscribed. In the lungs the lesions are extensive, but a very definite cellular reaction is in evidence.

The description given in the autopsy abstract applied to a comparatively early type of pulmonary lesion (six to eight weeks). In the more advanced processes (three to four months) caseation has begun, nodular areas are more definitely outlined and their resemblance to tuberculosis is marked. In fact, advanced torula infections are said to simulate tuberculosis more closely than any other disease. In some instances the presence of the yeast cell furnishes the only distinguishing criterion.

Lesions in the brain, liver, kidneys and spleen present much the same picture as described for the lung. The difference is mainly a quantitative one. As stated before, the brain exhibits very little cellular reaction against the advancing infection and the appearance for that reason is slightly altered. The gelatinous substance is produced more abundantly in nervous tissue than elsewhere. This substance is a product of the metabolism of the organism itself growing in living tissues and is not a result of the lytic action of the yeast on the tissue cells. Some strains when first placed on artificial media continue to produce small quantities of a mucoid material for one or two generations. This characteristic is never exhibited in old cultures. A noteworthy feature of the microscopical picture is the almost complete lack of regressive changes or evidence of necrosis around the focus of infection. It seems fair to assume, in view of this fact, that there is little or no toxemia, the chief damage being from the local destruction of tissue. Furthermore, this destruction is accomplished by the lysis of the tissue cells by the slowly advancing infection. The damaged tissue or organ may then undergo proliferative changes leading to repair, but the mode of action of the infectious agent does not elicit the usual fixed tissue reaction. This lytic reaction of the organism has brought forth the suggestion that the name *Torula histolytica*¹⁵ be applied to it.

It is evident that the subsequent tissue repair may lead, in organs like the brain and lungs, to more serious dysfunction than that caused by the original lesions.

PATHOGENICITY FOR ANIMALS AND MAN. Brewer and Wood¹⁹ report the only authentic case in which recovery occurred from a torula infection in man. Stoddard and Cutler believe, however,

that many infections occur which result in recovery, the true nature of the disease being unsuspected. Other writers fail to concur in this idea and look upon this as upon all other fungus infections as of very grave import. The latter view seems to be best supported by the facts. White mice and rats show a definite susceptibility to torula. This is true whether the organism is introduced by the intravenous or intraperitoneal route. The lesions produced are comparable to those found in man. In rabbits lesions in the central nervous system usually produce death in three to four weeks. If inoculated intraperitoneally typical lesions develop in the viscera, but the rabbits rarely succumb. This fact, established by the earlier workers, has been confirmed by our experiments. Dogs and guinea-pigs are relatively resistant.

NOMENCLATURE. As previously stated, the nomenclature of yeast infections has been indefinite and unscientific, the terms being applied loosely and without regard to their true botanical meaning. The chief error is the use of the term blastomycosis as a blanket expression covering all forms of fungus infection. Inspection of Table II will serve to orient the reader in regard to the position of torula in the botanical family tree. This classification is after Klocker¹⁸ and Weis,² somewhat modified by I. F. Lewis, of the Department of Biology, University of Virginia. The fungi represent a subphyllum of thallophyta, or plants without complex tissue structure. The fungi in turn are divided into the eumycetes, or true fungi, and the schizomycetes (fission fungi), in which class the bacteria are found. Grouped under the eumycetes are the phycomycetes, or algal fungi, and the mycomycetes. The algal fungi produce a tubular non-segmented mycelium, while the mycelium of the mycomycetes is divided by cross walls. The latter class includes the ascomycetes characterized by the formation of ascospores and the Fungi imperfecti. This heterogeneous collection is comparable to the chemical group known as lipoids in the fact that it contains numerous members not necessarily related but having several characteristics in common. In this large and poorly defined class torula occupies a prominent position.

By definition torula* is a yeast which multiplies by budding, does not produce ascospores, does not ferment carbohydrates and does not produce a mycelium in tissue or on culture.

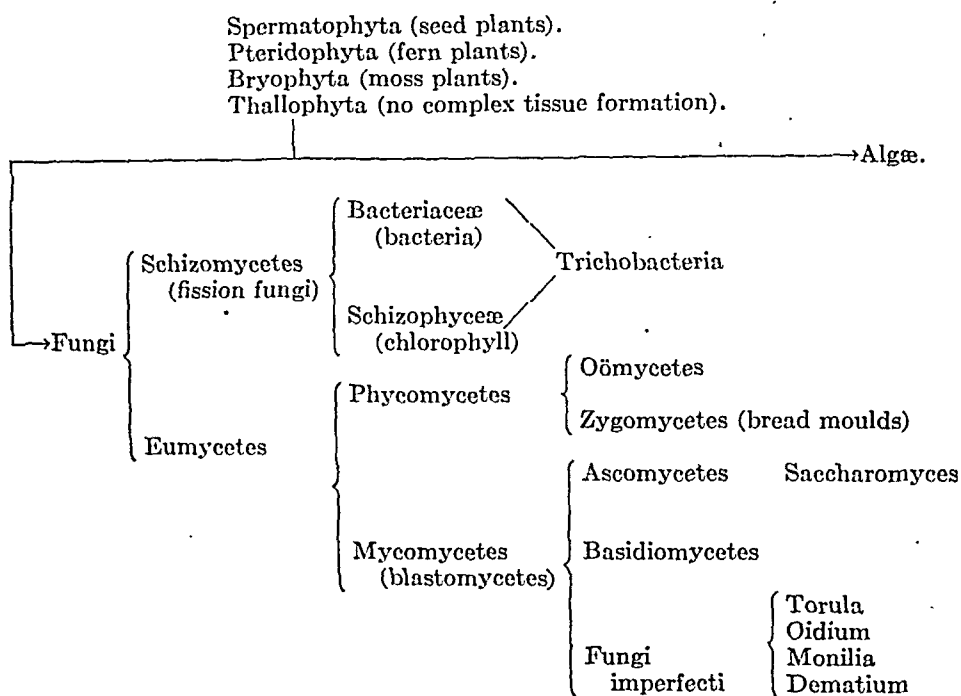
The next member, oidium, is by definition a yeast which multi-

* The author is aware that this definition of torula does not agree with that of Saccardo²² and other older writers who maintain that the organism is always black and may form hyphæ. The term however is applied to the class of organisms described above by more recent botanists and medical authors; and hence it is deemed best to retain it to avoid confusion. Furthermore the lack of differentiating characteristics of the organisms, prevents its being placed in one of the better defined divisions and further justifies the use of the term in medical literature.

plies by budding, does not produce ascospores, does ferment certain carbohydrates and does produce a mycelium when growing in culture. This is the organism which Gilchrist found to be the cause of his "blastomycetic dermatitis" and which is found relatively frequently in systemic infections.

In regard to the ascomycetes, *Saccharomyces cerevisiæ* was described by Busse as occurring in a few systemic infections and named by him *Saccharomyces hominis*. This is also the ordinary yeast of commerce and domestic science. The nomenclature of the moulds does not give rise to confusion and will not be considered here.

TABLE II.



CLINICAL FINDINGS. The clinical manifestations of torula infections are many and varied and call for the keenest of observation and reasoning on the part of the internist if a diagnosis is to be reached. When the central nervous system is the chief point of involvement, unusual and peculiar combinations of symptoms may be expected. Hemiplegias and monoplegias associated with cranial nerve involvements are frequent. All of the clinical signs of brain tumor may be present but efforts at localization of the tumor will fail. Decompression, if performed, usually provides only temporary relief and is soon followed by death of the patient. Stoddard and Cutler believe that the condition to which the name "pseudo-tumor" has been given is often in reality an unsuspected torula infection. In this condition a definite clinical picture of brain

tumor is presented, but no traces of a neoplasm can be found at operation or autopsy. The diagnosis of senile dementia and dementia paralytica has been made in 2 cases which proved to be torula infections.

When the cord is involved the pressure of the spinal fluid will be moderately raised. The yeast cells may usually be found in the fluid removed by lumbar puncture, but may be mistaken for leukocytes which they superficially resemble. A diagnosis of tuberculous meningitis is frequently made.

Regardless of where the principal focus of infection may lie, the toxemia is never profound. The temperature rarely rises above 101° F. and the leukocytes are but slightly increased (6000 to 9000), the small mononuclears being the predominating type.

If the infection is pulmonary, syphilis of the lung, lung abscess or tuberculosis may be suspected. There is a certain group of cases in every tuberculous sanatorium in which the sputum is consistently negative for the tubercle bacillus and yet the signs and symptoms of an active pulmonary tuberculosis are present. The author strongly urges that the sputum from such cases be cultured, with the idea of determining the presence or absence of pathogenic fungi. Such a study is especially desirable in cases in which the infection begins in the inferior lobes. The differential diagnosis from the auscultatory findings is impossible. It must be especially borne in mind that *torula* does not involve the skin and joints. A single case (Brewer and Wood) is recorded in which bone and muscle were involved. Certain indefinite "bodies," which from the description closely resemble torula cells, have been reported as occurring in the lymphogranulomas. In the future attempts by cultural methods should be made to confirm or discredit this apparent similarity.

ROENTGEN-RAY EXAMINATION. No reliable information is at hand in regard to roentgen-ray diagnosis. In the Virginia case the roentgenologist reported the lungs negative three weeks before death. It is likely, however, that if the patient survives for a longer time that some fibrosis will be demonstrable.

PROGNOSIS. Wade and Bel believe the infection to be nearly always fatal, while Stoddard and Cutler take a more optimistic view, assuming that many undiagnosed cases have gone on to recovery.

The author believes that more authentic cases involving the central nervous system have been reported, not because this system is more frequently involved, but because such involvements more frequently come to autopsy, thereby making a diagnosis possible. It seems fair to assume from the above that when the nervous system is invaded the prognosis is most unfavorable. On the other hand, pulmonary infections probably tend to recovery

and if properly handled the outlook is at least as favorable as in tuberculosis with an equal degree of lung involvement.

TREATMENT. In cases occurring in the central nervous system treatment is of little avail. Lumbar punctures for relief of pressure, an ice-cap to the head and potassium iodide up to 300 grains per day have been advocated. Decompression is contraindicated. The author is anxious to try the effect of the tartrates which have recently proved so effective against leishmaniasis but the opportunity has not yet presented itself. The pulmonary cases should be placed upon the usual antituberculous regimen with the addition of large doses of the iodides. Arsphenamine is without value.

Procedure Suggested for Isolation of Torula in Pure Culture. The material sent to the laboratory for examination from suspected cases of torula infection usually consists of spinal fluid, sputum or autopsy material.

1. Preparation of material: Smears from the untreated material should be made and stained with methylene blue. If the material is spinal fluid or sputum, centrifuge, wash and suspend organisms in salt solution. If material is from autopsy divide the tissue into small blocks, 2 x 4 cm., and pass through five rinsings of sterile salt solution.

2. Culture media: Inoculate the following media (stroke plates): 0.3 per cent lactic-acid-potato agar and 0.3 per cent lactic-acid-glucose agar. Stroke four plates of each, incubating two at 37°C. and two at 23°C. Incubate at least ten days before recording the plate as negative.

The lactic acid inhibits the growth of bacteria but does not interfere with the development of the fungi. Potato and glucose seem to be especially favorable for the growth of torula.

Inoculate a rabbit intravenously with 2 cc of a heavy suspension of the organism which has been heated to 53°C. for twenty minutes to kill bacteria. Inoculate a white rat intraperitoneally, using the same dosage. Sacrifice animals at the end of three weeks. Culture the brain, liver, lungs, spleen and kidneys as routine without regard to the presence or absence of macroscopical lesions. From the plates first inoculated, make subcultures on Sabouraud's agar; nutrient agar, pH 6; Löffler's blood serum.

Torula cells may be readily mistaken for lymphocytes when first seen in fresh material. This difficulty is easily overcome by the use of Wright's stain, as the several components of the yeast cell are not differentiated by this stain, in sharp contrast to the well-defined nucleus and cytoplasm of the blood cell.

Oidiomycosis (blastomycosis) is so frequently confused with torula infections that a table of differential points is appended.

TABLE III.—DIFFERENTIAL POINTS BETWEEN TORULA INFECTION AND OIDIOMYCOSIS (MODIFIED FROM STODDARD AND CUTLER).

Torula infection.	Oidiomycosis (usually called blastomycosis).
Cell wall.	Stains diffusely and easily with methylene blue and hematoxylin.
Size.	1-13 microns.
Reproduction.	By budding often producing small organisms which bud before enlarging.
Occurrence.	Always with a clear zone about it produced by gelatinous material.
Cell products.	A gelatinous material which often fills the lesion.
Character of lesions.	1. Lesion with solution of tissue filling with gelatinous material, slight chronic reaction.
	2. Nodules with or without caseation composed of epithelioid cells, giant cells and lymphoid cells. Caseation occurs centrally and apparently depends on the action of the cell products.
	No collection of polymorphonuclear cells, at any stage. No cutaneous lesions.
Clinical course in man.	A chronic disease without constant or great fever or leukocytosis.
Organs affected.	Brain and meninges; lungs; liver; spleen; kidneys; not skin or bones.
Reaction to treatment.	Not helped by arsphenamine. No real data as to effect of iodides.
Pathogenicity for animals.	Marked for mice and rats, slight for guinea-pigs, rabbits and dogs.
Organs affected in intraperitoneal inoculation.	Brain; lungs; liver; spleen and kidneys. Occasionally peritoneum.
Organism in culture.	Reproduces by budding, never produces mycelium. Does not ferment sugars.
	Does not stain as a rule with methylene blue or hematoxylin. Occasionally in deep stained preparations it takes a faint stain.
	4-20 microns.
	By budding, usually the bud is $\frac{1}{2}$ to $\frac{2}{3}$ the size of the parent cell and grows to the original size before it reproduces.
	No clear zone except in rare cases in the bone marrow.
	No gelatinous material.
	No such lesions.
	Nodules with or without caseation. Is apparently secondary to a crowding of cells.
	Abscesses deep and superficial with many polymorphonuclears. Miliary epidermal abscesses.
	A chronic skin disease or general infection with fever and leukocytosis.
	All organs, always the skin, often the bones.
	Usually improved by iodides.
	Slight or absent for all animals tried.
	Most marked in peritoneum, occasionally in lungs, not in central nervous system.
	Always grows mycelium sooner or later. Ferments some sugars.

Summary. 1. A search of the literature reveals only ten authentic cases of torula infection in man. An eleventh case is reported.

2. The morphology and cultural characteristics of the organism are described.

3. The infection occurs chiefly in the lungs and central nervous

system. In the former tuberculosis is simulated, while in the latter the clinical picture of a brain tumor is often presented.

4. The prognosis of the disease is unfavorable.

5. Methods of laboratory diagnosis are discussed.

6. An attempt is made to clarify the nomenclature of the fungus infection. Three main types are recognized:

(a) Saccharomycosis.

(b) Oïdiomycosis.

(c) Torulosis.

Conclusions. It is likely that torula infections in man are much more frequent than has heretofore been suspected and that a better understanding of the growth requirements of the organism will result in its more frequent recognition clinically. It is quite possible that certain obscure disease processes of the central nervous system, the lymph glands and the lungs may prove to be manifestations of this rather unusual virus.

The poor results from surgery if the infection is in the central nervous system, and the necessity for differentiation from tuberculosis in the pulmonary type, make an early diagnosis essential if a rational treatment is to be developed.

It is essential that a definite system of nomenclature for the fungus should be adopted and adhered to. The cutaneous disease called by Gilchrist "blastomycosis" is produced by oïdium and it would seem logical to refer to the infection as oïdiomycosis. It is suggested that the disease occurring in the lungs and central nervous system produced by a non-sporulating, non-fermenting, non-mycelium-producing yeast be known as torulosis.

NOTE.—The author wishes to express his thanks to Miss Mary G. Constable for valuable assistance rendered in carrying out the many technical procedures described above.

BIBLIOGRAPHY.

1. Marshall, Sheppe and Glass: University of Va. To be published later.
2. Weis: Jour. Med. Res., 1902, 7, 280.
3. Nichols: Jour. Med. Res., 1902, 7, 312.
4. Greenough: Jour. Med. Res., 1902, 7, 360.
5. Busse: Centralbl. f. Bakteriöl., 1894, 16, 175.
6. Curtis: Ann. de l'Inst. Pasteur, 1896, 10, 449.
7. Gilchrist: Bull. Johns Hopkins Hosp., 1896, 1, 270.
8. Gilchrist and Stokes: Jour. Exper. Med., 1898, 3, 53.
9. Wolbach: Boston Med. and Surg. Jour., 1915, 172, 94.
10. Wade and Bel: Arch. Int. Med., 1916, 18, 103.
11. Stoddard and Cutler: Torula in Man, Monograph, Rockefeller Inst. for Med. Res., January 31, 1916, No. 6.
12. Evans: California State Jour. Med., Torula Infection, 1922, 20, 383.
13. von Hansemann: Verhandl. d. deutsch. path. Gesellsch., 1906, 9, 21.
14. Türk: Arch. f. klin. Med., 1907, 90, 335.
15. Buchanan: Household Bacteriology, New York, Macmillan Co., 1913.
16. Stevens: The Fungi Which Cause Plant Disease, New York.
17. Duggar: Fungous Disease of Plants, New York.
18. Klocker: Die Gärungsorganismen in der Theorie und Praxis der alkohol-gärungs-gewerbe, Stuttgart, 1900.

19. Brewer and Wood: *Ann. Surg.*, 1908, 48, 889.
20. Ricketts: *Jour. Med. Res.*, 1901, 6, 377.
21. Irons and Graham: *Jour. Infec. Dis.*, 1906, 3, 666.
22. Ophuls: *Jour. Exper. Med.*, 1901, 6, 443.
23. Brown: *Jour. Am. Med. Assn.*, 1901, 48, 743.
24. Brown and Cummins: *Arch. Int. Med.*, 1915, 15, 608.
25. Jackson: *Jour. Am. Med. Assn.*, 1915, 65, 23.
26. Hektoen: *Jour. Am. Med. Assn.*, 1907, 49, 1071.
27. Montgomery and Ormsby: *Arch. Int. Med.*, 1908, 2, 1.
28. Stober: *Arch. Int. Med.*, 1914, 13, 509.
29. Wade: *Jour. Infec. Dis.*, 1916, 18, 618.
30. Frothingham: *Jour. Med. Res.*, 1902, 8, 31.
31. Rusk: *Systemic Oidiomycosis*, Univ. of Calif., *Publications in Path.*, 1912, 2, 47.
32. Saccardo: *Syllage Fungorum*, vol. 4, Padura, 1886.

THE RELATION OF THE NON-PROTEIN NITROGEN OF THE BLOOD TO PARATHYROID TETANY.

BY RUSSELL L. HADEN, M.D.,

AND

THOMAS G. ORR, M.D.

KANSAS CITY, KANSAS.

(From the University of Kansas School of Medicine, Kansas City, Kansas.)

TETANY is observed in a number of seemingly widely unrelated conditions. It may occur after parathyroidectomy; during pregnancy and lactation, associated with gastro-intestinal disease; in childhood, especially with rickets; in the course of certain infections and intoxications, or as an idiopathic disease. The bulk of evidence tends to show that it is a manifestation of a disorder of either mineral or protein metabolism. The symptoms are due to an increased irritability of the neuromuscular mechanism associated with changes in the nerve endings in the muscle. There must be a toxic substance arising somewhere in the organism which is common to the various conditions in which tetany occurs.

Research concerning the cause of tetany has centered largely around three theories: (1) That it is due to a disturbance in acid-base balance; (2) a deficiency in calcium; (3) an intoxication from certain protein derivatives, probably of the guanidin group. Tetany may occur when there is an increased amount of sodium bicarbonate in the blood. Thus it has been observed in man by Harrop¹ and others following the injection of large amounts of sodium bicarbonate, in pyloric obstruction in which there is typically an increase in the plasma bicarbonate,^{2 5} and following prolonged forced hyperpnea.³

Wilson, Stearns and Thurlow⁴ were the first to suggest that para-

thyroid tetany also is a manifestation of an alkalosis. McCann⁵ reported the finding of an increase in the CO_2 combining-power of the plasma of the blood of parathyroidectomized dogs. Hastings and Murray⁶ and Underhill and Nellans,⁷ in more extensive studies, have, however, been unable to verify McCann's results. Greenwald⁸ has recently subjected the evidence for a causal relationship between alkalosis and tetany to a critical review. He emphasizes that the individuals who developed tetany after the administration of bicarbonate suffered from renal deficiency. The tetany following prolonged hyperpnea he considers as due to tissue asphyxia. Greenwald concludes that the tetany associated with an increase in the bicarbonate of the blood is due, not to alkalosis, but to sodium poisoning, a disturbance due to an excess of sodium, and a loss of the normal equilibrium between sodium and other ions.

The relation between calcium metabolism and tetany has been emphasized by McCallum and his co-workers.⁹ In parathyroid tetany there is a marked diminution of blood calcium. Similar findings have been demonstrated in the idiopathic tetany of infants. Typical tetany may occur, however, in other conditions in which there is no calcium deficiency.¹⁰ Howland and Marriott¹¹ consider that the symptoms of tetany in children are directly referable to a low level of calcium in the blood. The calcium deficiency they recognize, however, as not being a primary condition. They think that *some factor, at present unknown, causes a reduction in the calcium of the blood.* It would seem equally possible that the toxic body might be neutralized and rendered ineffective by the calcium, and here would not act to produce tetany until the available calcium was exhausted. Such a possibility would explain equally well the beneficial effects of calcium administration in certain types of tetany. Haden and Orr¹² have shown that the toxic body in intestinal obstruction causes a marked reduction in blood chlorides. The toxic effects are not manifested until the chlorides are reduced below a certain level, and may be prevented entirely by providing chlorides in sufficient quantity.¹³ It would seem that the chlorides bear a relation to the toxic agent in intestinal obstruction analogous to that of calcium to the toxic substance in parathyroid tetany.

The evidence for a disturbance in protein metabolism as a cause for tetany has been presented by Paton and his collaborators.¹⁴ Following the demonstration by Koch¹⁵ that methyl guanidin and related bodies occur in the urine of dogs after parathyroidectomy, these workers showed that all the characteristic symptoms of tetany are produced by the intravenous injection of guanidin and of methyl guanidin. Similarly, Nathias and Sharpe¹⁶ have reported cases of idiopathic tetany in man, in which these bodies were demonstrable in the urine, and they conclude that tetany is a

manifestation of a guanidin and methyl guanidin intoxication. They believe that all true tetany has a common origin regardless of the clinical condition with which it may be associated.

It would seem that tetany must be explained by some factor which is common to the different conditions in which it occurs. Alkalosis is certainly not a necessary factor. Likewise, calcium deficiency occurs only in certain types. The question arises as to whether there is a common disturbance in the protein metabolism. It has long been known that the excretion of nitrogen and ammonia is increased after parathyroidectomy. Such observations have been made by Greenwald,¹⁷ Cooke,¹⁸ Hunter¹⁹ and Wilson, Stearns and Janney.²⁰ This increase has usually been explained as due to an accelerated metabolism incident to exaggerated muscular activity. It has been emphasized, however, that it may occur in parathyroidectomized dogs before the onset of tetany,¹⁸ or even in the entire absence of tetany.¹⁰ Togawa²¹ has studied the total non-protein nitrogen of the blood of puppies before and after parathyroidectomy. A single determination after operation showed a constant increase over one made before operation.

Our interest in the subject was aroused by finding that in experimental pyloric obstruction, in which tetany not uncommonly develops, there is a marked protein destruction and an increase in the non-protein nitrogen of the blood coincident with an alkalosis.²² The alkalosis seems to be incidental to the disturbance in protein metabolism. Similarly, tetany has been observed in dogs with experimental intestinal obstruction—a condition characterized by increased protein destruction. On the other hand, an extreme alkalosis has been repeatedly observed in animals without the development of tetany. One animal with a marked alkalosis in which a toxemia was prevented until death from secondary causes, twenty-eight days after the obstruction was made, showed no signs of tetany. Such observations have emphasized the importance of a disorder of protein metabolism as giving rise to the causative agent of tetany.

It would seem that if there is a disorder of protein metabolism following parathyroidectomy such changes should be reflected in the blood. The only experimental data on this point are those of Togawa,²¹ quoted above. With such ideas in mind, we have followed the level of the non-protein constituents of the blood of the dog following complete removal of the thyroid and parathyroid.

Methods. Full-grown dogs were used throughout the experiments. All operations were done under ether anesthesia with aseptic technic. The animals were kept in metabolism cages and were given no food after operation or for forty-eight hours preceding operation. They were allowed water *ad libitum*. Blood

for chemical analysis was obtained from the jugular vein before operation and at twenty-four-hour intervals thereafter until death.

The non-protein nitrogen and creatinine were determined by the method of Folin and Wu;²³ the amino-acid nitrogen by the method of Folin;²⁴ the carbon dioxide combining-power by the method of Van Slyke;²⁵ the urea nitrogen by the Van Slyke and Cullen modification²⁶ of the Marshall method; uric acid by the method of Benedict.²⁷ The chlorides were determined on the tungstic acid filtrate in the manner suggested by Gettler.²⁸

Experimental Observations. In 2 animals only the anterior parathyroids were removed. The animals showed no untoward symptoms at any time and serve as controls on the blood chemical findings of the animals in which all parathyroid tissue was removed. The results of the blood analyses of the 2 animals with partial parathyroidectomy are shown in Table I: The total non-protein nitrogen did not rise following operation, but gradually fell, due to starvation. The other substances determined show little of interest. The animals recovered completely.

TABLE I.—EFFECT OF PARTIAL PARATHYROIDECTOMY ON THE BLOOD OF THE DOG.

Dog No.	Day after operation.	Amount per 100 cc.							CO ₂ combining-power, volume per cent.	Remarks.
		Non-protein nitrogen, mg.	Urea nitrogen, mg.	Uric acid, mg.	Creatinine, mg.	Amino-acid nitrogen, mg.	Sugar, mg.	Chlorides, mg.		
26	0	24.8	5.6	1.3	1.2	6.4	54	540	43.8	No tetany at any time. Recovered.
	1	29.7	9.8	2.0	1.1	6.3	59	400	30.5	
	2	27.7	8.4	2.0	1.1	6.3	110	460	38.1	
	3	22.7	6.5	2.8	1.1	5.8	47	430	40.0	
	4	20.2	5.1	4.0	1.4	5.2	49	480	49.7	
	6	21.4	5.6	4.0	1.4	5.6	..	480	38.1	
28	0	24.0	11.7	1.3	1.3	5.1	90	500	33.4	No tetany at any time. Recovered.
	1	23.6	11.7	1.2	1.2	4.8	57	420	32.4	
	2	18.6	8.4	1.1	1.1	4.0	90	480	48.5	
	3	17.2	7.5	1.0	1.0	5.0	69	430	52.2	
	4	23.0	8.9	1.1	1.1	4.6	54	420	46.6	

The blood chemical findings in 5 dogs in which the thyroid and parathyroids were completely extirpated are shown in Table II: Dogs Nos. 31, 33, 34 and 60 all developed symptoms of tetany and died in from three to ten days after operation. These 4 animals showed a definite though slight increase in non-protein nitrogen and urea nitrogen. The increase was coincident with the onset of tetany. The other non-protein bodies showed practically no

change. Two animals, Nos. 31 and 33, showed a slight increase in amino-acid nitrogen. The increase in nitrogen was almost

TABLE II.—EFFECT OF COMPLETE THYROPARATHYROIDECTOMY
ON THE BLOOD OF THE DOG.

Dog No.	Day after operation.	Amount per 100 cc.							CO ₂ combining-power, volume per cent.	Remarks.
		Non-protein nitrogen, mg.	Urea nitrogen, mg.	Uric acid, mg.	Creatinine, mg.	Amino-acid nitrogen, mg.	Sugar, mg.	Chlorides, mg.		
31	0	30.9	10.7	2.4	1.3	5.0	91	450	28.7	Tetany.
	1	21.8	6.5	2.0	1.4	4.5	87	470	34.3	
	2	31.2	13.5	2.5	1.4	4.6	83	490	32.4	
	3	30.6	12.6	2.0	1.5	5.0	62	480	35.3	Drowsy.
	4	32.3	13.1	2.0	1.5	4.3	87	480	29.6	
	5	24.0	9.8	1.3	1.3	3.8	91	480	34.3	
	6	25.4	14.9	1.4	1.1	4.5	85	480	32.4	Tetany.
	7	38.5	20.1	1.2	1.1	4.8	103	460	27.7	
	8	38.9	11.2	2.1	1.1	6.0	86	490	16.4	
33	9	40.0	23.8	1.3	1.5	6.0	125	460	28.7	Died.
	0	33.0	13.1	1.6	1.1	6.0	52	460	30.5	
	1	29.7	12.6	1.0	1.1	5.8	51	460	30.5	
	2	36.1	17.8	1.4	1.3	7.4	74	440	40.9	Tachypnea and muscle tremors.
	3	31.6	9.3	1.6	1.4	5.2	79	460	41.9	
	4	30.9	9.3	2.9	1.2	4.5	68	480	26.8	
	5	32.3	12.1	1.6	1.2	4.3	69	490	30.5	Died.
	6	29.7	9.4	2.2	1.2	6.5	81	480	34.3	
	7	30.0	9.8	4.8	1.3	6.5	100	460	27.7	
34	8	31.2	11.7	7.7	..	460	32.4	Tetany.
	0	23.6	14.9	2.9	1.2	6.5	106	410	26.8	
	1	33.6	12.6	2.3	1.1	6.5	90	410	29.6	
60	2	38.9	12.1	1.4	1.7	6.6	79	420	32.4	Tetany; died.
	3	37.0	14.9	1.1	1.3	6.0	90	420	34.3	
	0	29.1	10.3	3.6	1.8	6.2	83	490	37.2	
61	1	37.9	16.4	3.8	1.6	5.9	105	500	36.2	Tetany.
	2	29.7	15.4	3.1	1.0	5.2	79	480	40.0	
	3	26.5	9.8	3.6	1.0	5.2	78	470	47.5	
	4	27.7	9.3	3.2	1.0	5.0	86	500	36.2	
	5	45.1	20.1	2.7	1.2	6.0	74	530	36.2	
	6	34.0	12.6	1.4	1.4	5.5	77	420	35.3	
	7	27.5	6.0	1.8	1.6	5.7	86	520	32.4	Died!
	8	27.7	8.9	1.5	1.4	5.7	81	490	41.9	
	9	30.6	9.8	2.1	1.4	5.5	105	490	40.0	
	0	26.1	9.3	3.0	1.0	6.0	54	470	40.0	Drowsy.
	1	27.7	8.4	2.7	1.3	6.4	47	440	40.0	
	2	23.4	4.7	2.4	1.2	7.5	48	430	38.1	
	3	20.4	2.3	1.4	1.3	7.5	57	460	30.5	No tetany at any time.
	4	26.5	8.4	2.7	1.2	6.2	100	450	36.2	
	5	23.4	6.1	1.4	1.3	5.5	85	470	36.2	
	7	22.2	7.0	2.8	1.0	5.8	93	540	38.1	Died.

entirely in the urea nitrogen and undetermined nitrogen. The chlorides remained practically constant throughout. There was little change in the carbon dioxide combining-power. Our findings are in accord with those of Hastings and Murray⁶ and Underhill and Nellans,⁷ who have found no indication of an alkalosis in dogs following parathyroidectomy.

In rather marked contrast to the findings in animals who showed symptoms of tetany are the results in 1 animal which died on the eighth day after complete parathyroidectomy. This animal showed no symptoms of tetany, but continued in a state of drowsiness. The non-protein nitrogen fell to a very low level. The urea nitrogen on the fourth day was the lowest we have so far seen in several hundred urea-nitrogen determinations on over 100 experimental animals. The other chemical changes were of little interest. It has been emphasized by numerous workers that there is a marked disturbance of metabolism after parathyroidectomy. This occurs apart from the development of tetany.

Discussion. Our findings indicate that the one constant change in the blood of the dog after parathyroidectomy in animals which develop tetany is a definite increase in the total non-protein nitrogen. The increase is almost entirely limited to the urea nitrogen and undetermined nitrogen. Such findings are characteristic of the blood chemical changes observed in other types of toxemia, which we consider as due to a disorder of protein metabolism. The uric acid, creatinine and amino-acid nitrogen have shown no constant change. The CO_2 combining-power has shown relatively little variation. The chlorides have remained at almost a constant level. The sugar has shown little of interest.

Summary. 1. Daily blood chemical analyses are reported on 7 dogs subjected to operation on the parathyroid glands.

2. Two animals had only the two anterior parathyroids removed. Five animals had a complete thyroparathyroidectomy.

3. Four animals with complete parathyroidectomy developed tetany. One animal died on the eighth day without showing tetany.

4. The 2 with only the anterior parathyroids removed and the 1 with complete parathyroidectomy, which did not develop tetany, showed no increase in total non-protein nitrogen in the blood.

5. The 4 animals showing tetany all showed an increase in urea nitrogen and undetermined nitrogen. The increase was demonstrable before the onset of tetany.

6. The uric acid, amino-acid nitrogen, creatinine, sugar, chlorides and CO_2 combining-power showed no constant change.

7. These findings lend some support to the theory that tetany is a symptom due to some toxic body arising in the course of a disorder of protein metabolism.

BIBLIOGRAPHY.

1. Harrop, G. H.: *Bull. Johns Hopkins Hosp.*, 1919, 30, 62.
2. McCallum, W. G., Lintz, J., Vermilye, H. N., Leggett, T. H., and Boas, E.: *Bull. Johns Hopkins Hosp.*, 1920, 31, 1. Grant, S. B.: *Arch. Int. Med.*, 1922, 30, 355.
3. Grant, S. B., and Goldman: *Am. Jour. Physiol.*, 1920, 52, 209.
4. Wilson, D. W., Stearns, T., and Thurlow, M. De G.: *Jour. Biol. Chem.*, 1915, 23, 89.
5. McCann, W. S.: *Jour. Biol. Chem.*, 1918, 35, 553.
6. Hastings, A. B., and Murray, A. H., Jr.: *Jour. Biol. Chem.*, 1921, 46, 233.
7. Underhill, F. P., and Nellans, C. T.: *Jour. Biol. Chem.*, 1921, 48, 557.
8. Greenwald, I.: *Jour. Biol. Chem.*, 1922, 54, 285.
9. McCallum, W. G., and Voegtlin, C.: *Jour. Exper. Med.*, 1909, 11, 118.
- McCallum, W. G., and Vogel, K. M.: *Jour. Exper. Med.*, 1913, 18, 618.
10. Tisdall, F. F.: *Jour. Biol. Chem.*, 1922, 54, 35.
11. Howland, J., and Marriott, W. McK.: *Quart. Jour. Med.*, Oxford, 1918, 11, 289.
12. Haden, R. L., and Orr, T. G.: *Jour. Exper. Med.*, 1923, 37, 365.
13. Haden, R. L., and Orr, T. G.: *Jour. Exper. Med.* (In press.)
14. Paton, D. N., and Findley, L.: *Quart. Jour. Exper. Physiol.*, 1917, 10, 203.
15. Koch, W. F.: *Jour. Biol. Chem.*, 1912, 12, 313.
16. Nathias, F. J., and Sharpe, J. S.: *Brit. Med. Jour.*, 1921, 2, 238.
17. Greenwald, I.: *Am. Jour. Physiol.*, 1911, 28, 103.
18. Cooke, J. V.: *AM. JOUR. MED. SC.*, 1910, 140, 404.
19. Hunter, A.: *Quart. Jour. Exper. Physiol.*, 1915, 8, 23.
20. Wilson, D. W., Stearns, T., and Janney, J. H.: *Jour. Biol. Chem.*, 1915, 23, 123.
21. Togawa, T.: *Jour. Lab. and Clin. Med.*, 1920, 5, 299.
22. Haden, R. L., and Orr, T. G.: *Jour. Exper. Med.*, 1922, 37, 377.
23. Folin, O., and Wu, H.: *Jour. Biol. Chem.*, 1919, 38, 81.
24. Folin, O.: *Jour. Biol. Chem.*, 1922, 51, 337.
25. Van Slyke, D. D., and Cullen, G. E.: *Jour. Biol. Chem.*, 1913, 30, 289.
26. Van Slyke, D. D., and Cullen, G. E.: *Jour. Am. Med. Assn.*, 1914, 62, 1558.
27. Benedict, S. R.: *Jour. Biol. Chem.*, 1922, 51, 187.
28. Gettler, A. O.: *Jour. Am. Med. Assn.*, 1921, 78, 1652.

THE ACTION OF INTRAVENOUS INJECTIONS OF SODIUM BICARBONATE UPON THE KIDNEYS.

BY ELLIS KELLERT, M.D.,

ALBANY, N. Y.

(From the Bender Hygienic Laboratory, Albany, N. Y.)

THE symptom-complex known as acidosis, which would perhaps be more properly called hypalkalinity, is a fairly common clinical condition. It occurs in a variety of metabolic and infectious disorders and frequently becomes of supreme importance in diabetes, nephritis, pneumonia, influenza and certain poisonings as by phosphorus and wood alcohol. The mechanism involved in bringing about an acidosis is exceedingly complex and while theoretically easy of explanation, is not always susceptible of proof, even experimentally.

The acidosis of diabetes, long recognized, has been in the past treated with alkalis chiefly in the form of sodium bicarbonate. In recent years we find this salt used intravenously in comparatively large amounts in combating the coma of diabetes, wood alcohol poisoning and certain infections as influenza, when the symptoms become severe. Since the acidosis is due to the improper or insufficient neutralization or elimination of the acids produced in excess in these diseases, it appears a logical procedure to introduce into the body alkali to replace that abstracted, the removal of which brings about the symptoms.

The excellent reported results in diabetes by the use of insulin may perhaps make the bicarbonate treatment of little importance, but in many other conditions accompanied by acidosis its use will continue. Since in any form of therapeutics it becomes of first importance to be certain that the treatment does no harm we must carefully consider those statements indicating that the use of sodium bicarbonate may be injurious.

Joslin¹ cautions strongly against the administration of alkali in diabetes feeling that the large amounts of acid salts which are formed overwhelm the kidneys. Grant² speaks of an alkalosis resulting from an overdose of sodium bicarbonate. Hardt and Rivers³ treating gastric ulcer by the Sippy⁴ method claim that toxemia and renal changes are brought about as a result of the treatment. King and Church⁵ noted that bicarbonate used intravenously inhibited intestinal movements. Of all the various contrary reports the important ones relate to a possible injurious action upon the kidneys and it is this phase of the subject which is of interest to us.

The quantity of sodium bicarbonate that may be given intravenously at one sitting is surprisingly large. In the treatment of sprue, Castellani⁶ "used intravenously 10 to 20 ounces of a 2 or 4 per cent solution given slowly every day or every other day until twelve injections had been given." Peabody⁷ in a case of uremia gave on successive days—300 and 700 cc of 4.7 per cent sodium bicarbonate and again 375 cc of 5 per cent solution with a favorable immediate response although death eventually ensued. Carey⁸ in the precoma stage of diabetes gave large quantities of bicarbonate by mouth and states that if necessary it may be given intravenously. Sellards and Shaklee⁹ as a routine in cases of cholera used 1.5 per cent bicarbonate intravenously in 2 liter quantities and in cases of collapse gave 4 liters. Harrop and Benedict¹⁰ treating a case of acute methyl alcohol poisoning gave 400 cc and the day following 500 cc of 5 per cent sodium bicarbonate intravenously. No untoward renal effects were observed. On another occasion Harrop¹¹ in a case of bichloride poisoning gave in two days 60 gm. of bicarbonate in the form of a 5 per cent solution.

Since the bicarbonate solutions are usually heated before injection

it has been thought that the sodium carbonate thus formed is highly irritating yet Graham¹² working with dogs reported no such action of sodium carbonate. MacNider¹³ found that sodium carbonate used intravenously protected the tubular epithelium against the action of anesthetics. Haskell, Heilman and Gardner¹⁴ gave boiled 5 per cent and 10 per cent solutions with no immediate ill results although they do state its use in this manner is very dangerous.

In the present investigation, young adult rabbits were used and injected with 5 per cent sodium bicarbonate in distilled water. Two animals were used for each experiment: One receiving unheated solution and the other an equal quantity of a similar solution heated in the autoclave for twenty minutes at 15 pounds' pressure. Preliminary examination of the urine in the first experiment over a period of seven days showed nothing abnormal. Twelve cubic centimeters of the solution were injected in each case intravenously. No marked changes were observed in the urine following the injections. Four days later the bicarbonate injections were again made, without demonstrable change. A repetition of the experiment on fresh animals gave like results so that we felt assured that the bicarbonate alone, heated or unheated, induced no renal changes.

These animals were chloroformed and the kidneys examined microscopically. "They appear normal in every respect. There are no glomerular changes, the tubular epithelial cells are well defined, the nuclei sharp and the cells not swollen. No debris and no cast-like objects are found in the lumina of the tubules."

Next to determine the influence of the bicarbonate on an injured kidney, the following experiment was performed: Each of two rabbits received subcutaneously 0.025 gm. of potassium chromate. On the third day the urine contained albumin (++) and numerous hyaline and epithelial casts. The sodium bicarbonate injections were administered as before and without apparent ill effects. The albumin and casts quickly disappeared from the urine which became normal four days after the injections of bicarbonate. On the seventh day the animals were killed. The necropsy disclosed in each case a slight amount of fluid in the peritoneal cavity and kidneys which were congested and moderately edematous.

"Microscopical examination shows distinct evidence of renal injury. The glomeruli are distended and frequently lobulated. The tubular epithelial cells are granular, the margins poorly defined and the nuclei in many instances absent. The lumina of the tubules contain granular debris and casts. These changes, while present are moderate and not widespread throughout the kidneys."

In the next experiment, 2 full-grown rabbits were selected and after urine examinations over several days showing nothing abnormal, each received intravenously 15 cc of 5 per cent sodium bicarbonate, one solution being heated as above described. Each showed a faint trace of albumin but no casts. The albumin dis-

appeared the following day. Each animal was then injected subcutaneously with 10 cc of 1 to 1000 mercuric chloride (0.010 gm. HgCl_2). The animals became quite ill and the urine showed albumin (+++) hyaline, epithelial casts and leukocytes. Five days later with albumin and casts still abundant each rabbit received 15 cc of bicarbonate as before and the next day each received a similar amount or 30 cc in twenty-four hours. The rabbits remained well and the albumin and casts gradually disappeared. Later, in these same animals the bicarbonate injections were repeated twice but the urine steadily improved becoming normal.

The animals were killed and examined immediately. Each showed a slight amount of fluid in the peritoneum and congested kidneys. "Microscopically, few changes are seen. The glomeruli appear normal but show an increased number of nuclei. Few casts are present, but many of the epithelial cells are granular, poorly defined and the nuclei lost. Evidence of nephritis in these animals is present but not pronounced."

In the next experiment, 2 rabbits were each injected subcutaneously with 0.002 gm. uranium nitrate. This induced a prompt albuminuria, but without casts. Two days later 0.002 gm. were again injected and 0.005 gm. at the end of another two days. Albumin (+++) and hyaline casts were then found and the animals appeared ill.

Each rabbit now received intravenously 20 cc of 5 per cent sodium bicarbonate, one solution heated as before. No urinary changes followed and the bicarbonate injections were repeated in four days. The urine continued to improve, but never became normal. This experiment was repeated in another set of animals with like results.

On microscopical examination, the kidneys of these rabbits show marked changes. The glomeruli are distended, injected and lobulated. The nuclei are increased in number. "An occasional Bowman's capsule contains albuminous material. The epithelium of the tubules is fairly normal, but in some areas is flattened, granular and poorly defined. Here the lumina contain casts or granular debris. The casts or cast-like bodies are very numerous."

The urine of rabbits is normally alkaline, so as a final experiment 2 rabbits were maintained on a barley diet until the urine became faintly acid. Each then received 5 per cent sodium bicarbonate as in the above experiments. No urinary changes were observed. These same animals were continued on the barley diet and given daily subcutaneous injections of tenth normal hydrochloric acid until the urine became strongly acid. Each rabbit was then again given intravenously 10 cc of 5 per cent sodium bicarbonate. No urinary changes followed and the animals remained well.

Summary. We have given to apparently normal rabbits having normal urine intravenous injections of 5 per cent sodium bicarbonate

in quantities per kilo in excess of those usually given to human beings for therapeutic purposes. No injurious action could be seen on observation of the animals and examination of the urine.

In a series of rabbits also, with a nephritis brought about by injections of potassium chromate, mercuric chloride and uranium nitrate, similar use of sodium bicarbonate in equal or larger quantities unheated in one set and autoclaved in another, resulted in no ascertainable harmful action on the kidneys. The animals receiving the injections of the chemicals and sodium bicarbonate showed no greater renal changes than those receiving the chemicals alone.

There is thus no experimental evidence, in the case of rabbits, for the belief that intravenous injections of sodium bicarbonate as used for therapeutic purposes, are injurious to the kidneys.

REFERENCES.

1. Joslin: Treatment of Diabetes Mellitus, 1917, p. 394.
2. Grant: Arch. Int. Med., 1922, 30, 355.
3. Hardt and Rivers: Arch. Int. Med., 1923, 31, 171.
4. Sippy: Jour. Am. Med. Assn., 1915, 64, 1625.
5. King and Church: Am. Jour. Physiol., 1922, 62, 459.
6. Castellani: Brit. Med. Jour., 1921, 1, 338.
7. Peabody: Arch. Int. Med., 1915, 16, 963.
8. Carey: Jour. Am. Med. Assn., 1921, 76, 1393.
9. Sellards and Shaklee: Philippine Jour. Sci., 1911, 6, 53.
10. Harrop and Benedict: Jour. Am. Med. Assn., 1920, 74, 25.
11. Harrop: Bull. Johns Hopkins Hosp., 1919, 30, 62.
12. Graham: Arch. Int. Med., 1920, 25, 575.
13. MacNider: Jour. Exper. Med., 1916, 23, 171.
14. Haskell, Heilman and Gardner: Arch. Int. Med., 1921, 27, 71.

PALPATION OF THE SPLEEN.

By WILLIAM S. MIDDLETON, M.D.,

MADISON, WIS.

(From the Department of Clinical Medicine, University of Wisconsin.)

ENLARGEMENT of the spleen develops in the course of many of the acute infectious diseases. Acute splenic tumor may be one of the first significant physical findings in typhoid fever. The characteristic "ague-cake" spleen of chronic malarial infestation may cast the first light on an otherwise obscure clinical picture. Certain diseases of the hemolytopoietic system, as the leukemias, acholuric jaundice, Banti's disease and Gaucher's splenomegaly, are constantly attended by varying degrees of splenic enlargement. Chronic passive congestion, either locally in the portal circulation or as an expression of general heightened venous pressure, may determine splenic enlargement. In this connection extreme enlargement of the spleen in a case of "abdominal mumps"—pan-

creatic metastasis—in the University Infirmary some years past may be mentioned. This circumstance was explained on the basis of pressure of the acutely inflamed pancreas on the splenic vein passing immediately behind or through its head. Splenic tumor is frequently remarked in the various types of cirrhosis of the liver. In infancy, inherited lues or rickets may determine enlargement of this organ. Subacute endocarditis, infarction and abscess are less frequent causes of splenic enlargement.

From this cursory review of some of the conditions leading to enlargement of the spleen, the clinical importance of a determination of its size becomes apparent. Situated deeply in the left hypochondrium, the spleen is overlaid by the ninth, tenth and eleventh ribs, and in the main lies in the line of the tenth rib. Its upper pole may be normally placed opposite the ninth dorsal spinous process about 3 cm. from the vertebral column, while the lower pole may extend anteriorly to the mid-axillary or the anterior axillary line. "A line from the top of the sternum to the tip of the eleventh rib should be entirely anterior to the spleen."¹ The position of this organ high in the abdomen beneath the dome of the diaphragm renders it inaccessible to inspection and under normal conditions to ordinary methods of palpation. Percussion as a means of demarcating the splenic limits is rendered inaccurate through its anatomical relationships with the stomach, splenic flexure of the colon, left kidney and overlying lung.

The spleen is normally palpable in children only. Two circumstances other than splenic enlargement may, however, lead to its palpability in the adult, namely, elongation of its ligaments of attachment (floating spleen) and a marked intrapleural accumulation (pus, blood, serum or air). Since these latter circumstances admit of ready differentiation and elimination, a palpable spleen in the adult in any but the unusual case means enlargement.

Following the planes of least resistance the spleen enlarges forward and downward. Although the spleen by reason of its depth and smaller dimensions is less responsive to the respiratory movements than is the liver, yet the lower level assumed by the spleen on phrenic contraction forms the logical point of attack in palpation. The simplest palpatory procedure after the usual precautions of moderate flexion of thighs on trunk and legs on thighs, slight elevation of the head and quiet breathing with open mouth, is to place the palpating hand on the abdomen with the radial border of the index finger parallel to the costal margin (Fig. 1). Gentle downward pressure is made avoiding sudden or vigorous effort. As the patient inspires, slight cephalad pressure is applied on the palpating hand. This procedure is repeated at varying levels, always paralleling the left costal margin.

¹ Piersol, G. A.: Human Anatomy, 1916, Philadelphia, p. 1787.

The obvious mechanical result of this described pressure on the anterior abdominal wall is a narrowing of the space, into which the enlarged spleen must descend on inspiration. The natural outgrowth of this principle of the creation of an abdominal wedge, apex down, was the application of a force posteriorly behind the

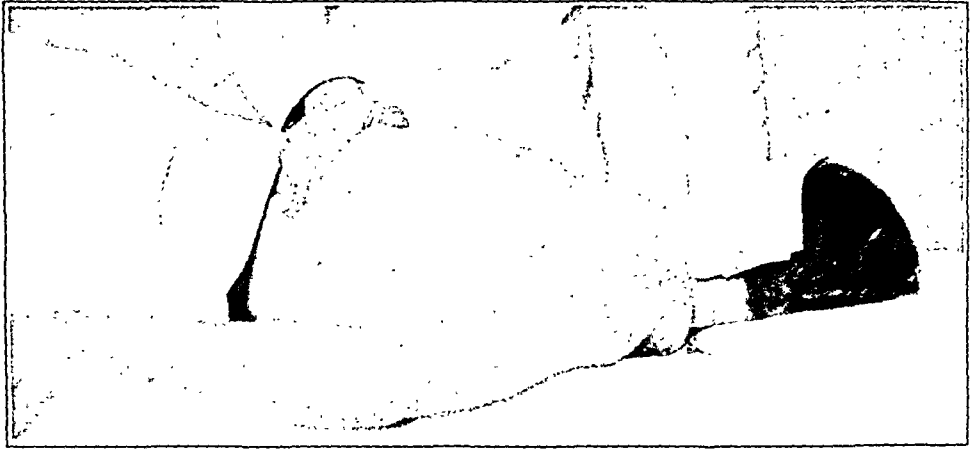


FIG. 1

floating ribs, since by their ready displacement anteriorly the zone of splenic descent would be still further narrowed. The customary method of producing this displacement of the eleventh and twelfth ribs is through the simple lift of the second palpating hand placed posteriorly (Fig. 2). The results with this method have been so far superior to those of simple anterior palpation as to lead to

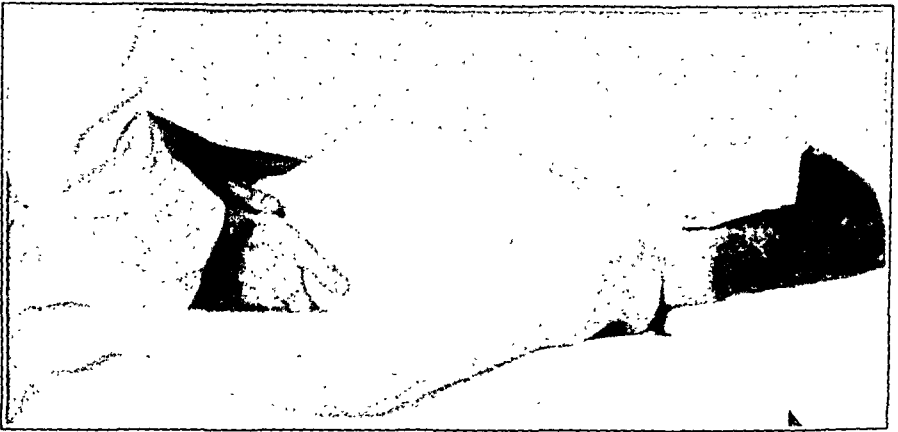


FIG. 2

a number of modifications. For instance it has been suggested that the knee of the examiner be placed posteriorly at the level of the eleventh and twelfth ribs, and the patient rolling against this obstruction replaces in effect the posterior palpating hand (Prof. J. A. Stengel).

The surprising readiness of palpation of an enlarged spleen in an adult whose forearm was carelessly left behind the back has led to a serious scrutiny of the applicability and relative merits of this method of examination. The customary collateral precautions for abdominal palpation are enjoined. The forearm is flexed at an angle of about 80 degrees and introduced behind the back as far as possible. With the patient lying on the forearm in this position, pressure is exerted over the tenth, eleventh and twelfth ribs as a rule. Both hands of the examiner are then free to palpate at the costal margins (Fig. 3) or one hand may be placed as in Fig. 1, while the second makes lateral pressure over the lower thorax and upper abdomen.

Three criteria of comparison with the usual methods of splenic palpation have resulted in a rather sweeping commendation of this procedure. Repeatedly spleens not palpable by any one of



FIG. 3

the described methods, including in addition to those considered above the right lateral and standing-bending positions, have been felt by this method. Almost invariably the ease of palpation of a doubtfully enlarged spleen by this procedure was in marked contrast to the results from the other methods. Lastly, comparison has been made of the frequency of the determination of splenic tumor in a given disease under the usual methods of palpation and by this plan. Osler² reports palpable spleen in 4 out of 23 cases (17.3 per cent) of acute catarrhal jaundice. Before applying the above described method of palpation, the figures for palpable spleen in this condition at the University Infirmary were 2 out of 13 cases (15.3 per cent). Since applying the method described, the spleen has been found enlarged in 19 out of 28 cases of catarrhal jaundice (67.8 per cent).

Such startling comparative data led to an examination of the

² Osler and McCrae: *The Principles and Practice of Medicine*, 1920, New York, p. 551.

probable points of mechanical advantage in the newer method. The most important factor in either method is apparently the amount of displacement effected. The thickness of the forearm of the patient obviously determines this factor in the newer method, while the height of the lift of the examiner is the deciding factor in the usual plan. In effect the lifting hand of the examiner is so placed as to create a lever of the second order through the involved ribs, while through the arm carried across the back the patient develops in its several points of application, first a lever of the second order and then approaching the vertebræ, one of the third order. A point of practical importance must become apparent in the latter relation, namely, given a measured degree of displacement, the closer the same is placed to vertebral column the greater will be the forward movement of the ends of the affected ribs. The individual variations would be so great that no effort has been made to determine the actual displacement at several points along the involved ribs. However, in a series of 10 adult males, the average displacement at the left posterior axillary line was 2.1 cm. greater on lying on the flexed forearm than by the customary lift. The procedure was controlled by taking the average lift of three separate examiners.

The second factor in importance in a comparison of the mechanics of the methods, is the force applied. In determining the force exerted by the lift of the posterior hand, all plans introducing a separate factor of displacement such as the arm cuff of the sphygmomanometer or the spring grip were rejected as leading to error. Two methods were eventually pursued and the results were comparable. First, the examiner stood on the platform scales and applying the usual force in his lift, the increase in weight on the beam was recorded. Then the reverse proposition was investigated. The examining table with the patient was placed on the platform scales and the decrease in weight on the lift of the examiner was noted. Using a series of adult subjects the average lift of 4 examiners was about 4 kg. At first thought this value seemed inconsiderable, and only a realization of the position in which the force is applied and the actual handling of a 4 kg. weight at arm's length lent force to the accuracy of this determination. To study the force exerted at the point of application of the posteriorly placed arm, a section was cut from the table corresponding to the transverse position of the arm, and beneath this loose section a balance was constructed (Fig. 4). This balance was so arranged that a rigid post placed at *A* and resting firmly on the platform of the scales (Fig. 5) would transmit the weight from the "floating" section (*c*) of the table to the scales (0.1 kg. on the reading beam = 1.66 kg. on the table balance).³ Observations showed for the individual a

³ Acknowledgment is gratefully made to Mr. J. S. Hipple for the construction of this device.

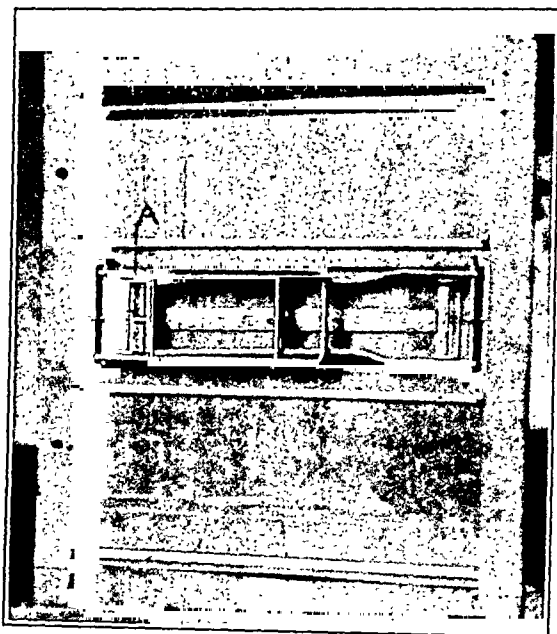


FIG. 4.—View of examining table from below.

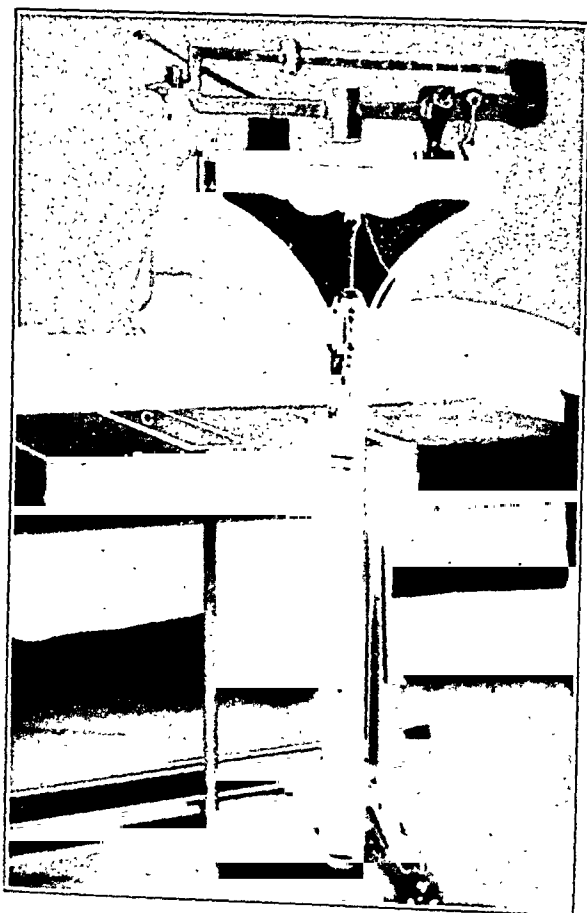


FIG. 5

constant advantage in force applied through the flexed arm placed posteriorly over the figure determined for the lift; but extreme variations dependent particularly on weight and spinal conformation made averages and groupings impossible. A significant observation in this relation was made with reference to the influence of flexion of the thighs and legs on the readings. Invariably as would be expected from the practical results, the pressure exerted after flexion of the thighs on the abdomen and legs on thighs was considerably greater than with legs in extension.

A third consideration, which unfortunately is incapable of calculation, is that of muscular resistance in the patient. Obviously the group in which greatest difficulty is encountered in palpation of the spleen, is the adult male. Furthermore, from experience it is this group in which the results from the new method of palpation are most gratifying. Can a partial explanation for this fact lie in the relatively lessened muscular resistance to a greater displacement from passive pressure in the arm placed posteriorly as compared with the active force of a lifting hand? Obviously, the factors of displacement, force and resistance, as represented by the two methods, approach as weight, development and muscular tone decrease; so that in the poorly nourished and muscled adult and in the child the mechanical advantages of the newer method are effaced.

Palpation of the liver and the kidneys are facilitated by this method.

Summary. A new method for palpation of the spleen is described in which the posteriorly placed flexed forearm of the patient supplants the examiner's hand in inducing anterior displacement of the lower ribs. This procedure apparently promises better results clinically and has certain obvious mechanical advantages over the usual palpatory methods. Since an optimum degree of anterior displacement of the tenth, eleventh and twelfth ribs would seem to determine the superiority of a given method, a padded, tapering roll or sand bag might be substituted for the arm in hospital practice; but for general practice this refinement is unnecessary.

REVIEWS.

DISEASES OF THE SKIN. By FRANK C. KNOWLES, M.D., Professor of Dermatology, Jefferson Medical College. Second edition. Pp. 600; 200 illustrations and 14 plates. Philadelphia and New York: Lea & Febiger, 1923.

THE author has met and overcome the difficult in improving an already good book and yet keeping it down to 600 pages. His text must appeal to the general practitioner because it is so arranged that he can first secure leads to the diagnosis by means of two keys (one based on the type of lesion exhibited and the other on the body-part affected) which are provided in early chapters; thereafter the physician is enabled to diagnose between these different leads by referring to the individual diseases which are described in later chapters. Its systematic arrangement is eminently suited to the student, and the descriptions of therapeutic procedures, particularly such special ones as the electrical, carbon dioxide snow, etc., are almost unique in their conciseness, yet sufficient.

W.

ORTHOPAEDIC SURGERY. By ROYAL WHITMAN, M.D., M.R.C.S., F.A.C.S., Surgeon to the Hospital for Ruptured and Crippled, New York. Seventh edition. Pp. 960; 877 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

THIS volume lives up to the reputation of the author, and depicts the progress of the subject up to the publication of the book. To the general practitioner it is of great value in enabling him to read and correlate symptoms and assist in early prevention of deformities and to give a well-formed opinion as to the prognosis of the condition under study. The more common conditions are thoroughly discussed and the choice of methods of treatment is given consideration, but the author deals at greater length on those methods which, in his experience, have been the most successful. The last chapter of the book, comprising ninety-two pages, is devoted to collateral orthopaedic surgery, supplanting the chapter on military orthopaedics. In this chapter the author gives the best methods for the best possible results to prevent an increase in the number of disabled or deformed.

B.

THE DIETARY OF HEALTH AND DISEASE. By GERTRUDE I. THOMAS, Instructor in Dietetics, University of Minnesota. Pp. 210; 7 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

THIS is an excellent book to use as a text in teaching. The fundamentals of dietetics are presented in such a way as to make it comprehensible to students who have no background of organic chemistry. So many books on diets are just plain cookery or else necessitate a knowledge of organic chemistry. Particularly good is the use of the outline form and the tabulation of material. The important points are easily grasped in this way. The chapters on special diets are excellent. Many diet books are inadequate in this respect. The bibliography at the end of each chapter is very helpful to both student and teacher. W.

BERGEY'S MANUAL OF DETERMINATIVE BACTERIOLOGY. Arranged by a committee of the Society of American Bacteriologists, consisting of DAVID H. BERGEY, Chairman; FRANCIS C. HARRISON; ROBERT S. BREED; BERNARD W. HAMMER; FRANK W. HUNTOON. Baltimore: Williams & Wilkins Co., 1923.

THE rapid progress in the science of bacteriology for the past twenty years or more has rendered previous classifications of bacteria somewhat unsatisfactory. This has been due partly to the discovery of new organisms and species and partly to the advance of cultural methods and study. Consequently morphological classifications in themselves have become outgrown and no classification can now approximate completeness without a detailed inclusion of the cultural characters. This manual has accomplished this end by offering a detailed outline of morphological and cultural descriptions and, as far as it is possible, the serological types of the various organism. In all, almost seven hundred organisms are described, and the descriptions readily lend themselves to the identification of unknown. Many new names and terms have been introduced, but they are distinct improvements, because once learned they include tell-tale features. For example, "bacillus" has always covered a multitude of organisms and, aside from stating an organism to be rod-shaped, was of little help. By this classification the bacilli have been subdivided and renamed, so that a "bacillus" is here an aërobic spore-bearing rod and a "clostridium" an anaërobic spore-bearing rod, etc. Perhaps the only criticism to be made is that it might have been of assistance to the student to have included in the index the old names, until at least the new names are better known. The committee is to be congratulated on this stupendous work, first for supplying a great need and second for attributing to the cultural characters a prominent role to their classification. J.

PRINCIPLES OF BACTERIOLOGY. By ARTHUR A. EISENBERG, A.B., M.D., Director of Laboratories, St. John's Hospital, Cleveland. Second edition. Pp. 214; 40 illustrations. St. Louis: C. V. Mosby Company, 1923.

THOUGH not so stated in the title, this book was obviously intended for nurses and women technicians. Nevertheless, it would have been desirable to include more of the bacteriological advances that have been made since the appearance of the first edition in 1918. For instance, Noguchi's work on yellow fever and rabies is not mentioned and both of these are included among diseases of unknown causation. Bull is not "now doing a most promising work on the serum treatment of gas bacillus infection," and Park and Plotz are not generally recognized as the discoverers "of the organism causing the typhus fever." As an example of method of presentation, eleven "diseases of unknown causation" are handled in three small pages. To the reviewer, at least, "Spallanagani" (p. 20) is a new and unknown scientist, and "geunao" (p. 22) a strange Greek root. It seems to be strange also to the author, as it later appears in the form "geneo" (p. 29). The change of the Greek word for red from "erythraios" to "erytheus" (p. 61) is another example of the carelessness typical of the booklet.

K.

WAR BLINDNESS AT ST. DUNSTAN'S. By SIR ARNOLD LAWSON, Senior Ophthalmic Lecturer on Ophthalmic Surgery, Middlesex Hospital. First edition. Pp. 150. London: Henry Frowde, Hodder & Stoughton, 1922.

THE author briefly reviews the medical work among the war blind at St. Dunstan's, from the latter part of 1914 until May of 1920, during which period most of those blinded in the Great War, both as the result of wounds and disease, had come to this hospital. It contains an analytical record of the wounds and diseases, as a result of which 825 men lost their sight. Blindness as a result of traumatism was due either to through-and-through wounds of the head, fractures of the skull, either in the occipital region or other localities, and concussion injuries. A number of the most interesting cases are briefly reviewed. He calls attention to the rarity of sympathetic ophthalmia in the Great War. Only 3 or 4 cases were seen at St. Dunstan's. This experience of the author is in agreement with the observations of other ophthalmologists dealing with the war wounded. The cases of blindness of non-traumatic origin amounted to the surprisingly large percentage of 25. This large proportion is explained by the author as due to the unusual physical and nervous strain incident to

war activities. He is convinced that, as a result of the change in environment, many cases of blindness developed far earlier than would have been the case in ordinary civil life. The chapter on the reëducation of the blinded soldier is most interesting. Never in the history of the world had such a large group of blind been brought together as at St. Dunstan's. The book is concluded with a chapter on the reëducation of the blind and contains many valuable suggestions relative to educational methods. After reading this chapter, one cannot help but agree with the author that blindness, far from being a "calamity, is but only an inconvenience."

B.

PHYSICAL DIAGNOSIS. By RICHARD C. CABOT, M.D., Professor of Medicine in Harvard University, formerly Chief of the West Medical Service at the Massachusetts General Hospital. Eighth edition. Pp. 536; 285 illustrations. New York City: William Wood & Co., 1923.

THE eighth edition of the author's work has been entirely reset and considerably enlarged. In the resetting he has taken the opportunity of completely revising the section on electrocardiography as well as adding a considerable increase in the amount of space devoted to roentgen-ray diagnosis of the chest and genito-urinary system. To the few who are unacquainted with the previous editions of the author's work on physical diagnosis, we have no hesitation in recommending it most heartily. It is one of the most lucid, thorough and sensible books that we know of. There is a real pleasure, for example, in reading over the chapter on diseases of the lungs to find that the author does not suggest making a diagnosis of pulmonary tuberculosis on the basis of a few questionable physical signs, a habit which many so-called experts in tuberculosis attempt, but, on the contrary, the author demands very definite physical signs before making the diagnosis. There is only one real criticism of the book, and that is the illustrations are decidedly hazy and lack the clear-cut appearance which enhances the value of any illustration.

M.

BLOOD CHEMISTRY (COLORIMETRIC METHODS). By WILLARD J. STONE, M.D., Attending Physician, Los Angeles General Hospital. Pp. 75; 4 illustrations. New York: Paul B. Hoeber, Inc., 1923.

THIS rather unusual book is a compilation of methods of accomplishing the various blood-chemical tests which are found of value in clinical work. In addition to this there is a short discussion

on the value of these tests, their indications and interpretation in disease. Oddly enough, the last portion of the book contains a full discussion of the dietary control of disturbances of metabolism, notably diabetes. The exact need for such a book is a question to the reviewer. The laboratory technicians may use it for reference because of its brevity and clearness in detailing technic, but probably, as they have been taught from more complete reference books, they would be more likely to refer to such books. The average practitioner of medicine will not have the time or facilities to carry out the tests, but, be that as it may, the fact is assured that the compilation is simple, easy and direct, and will be of value to those into whose hands it may fall if they are making laboratory studies. M.

ENDOCRINE DISEASES INCLUDING THEIR DIAGNOSIS AND TREATMENT. BY WILHELM FALTA. Translated and edited by MILTON K. MEYERS, M.D., Neurologist to the Northern Liberties Hospital, to the Lucien Moss Home, Jewish Hospital and to the Dispensary of the St. Agnes Hospital, Philadelphia. Third edition. Pp. 669; 104 illustrations. Philadelphia: P. Blakiston's Son & Co., 1923.

THE present edition of the author's work on the endocrine system is a revised edition of his former work entitled *The Ductless Glandular Diseases*, and as such is an improvement over the previous edition. The author takes up first a general discussion of the glands of internal secretion and then considers in detail diseases of the thyroid, parathyroid, thymus, pituitary and suprarenal, sexual glands, pluriglandular diseases, diseases of the pancreas and their relation to diabetes mellitus, and the different forms of obesity. From this short description of the contents of the volume it may readily be seen that all the known glands of internal secretion are discussed, and without detailing the work, it may be added by the reviewer, that the whole subject of endocrinology is considered most fully and most carefully. In looking over the book one is struck with the very sane method that the author deals with known facts of disease of the endocrine system and the most careful manner with which he dismisses from real consideration the tremendous amount of hypotheses and unproven facts with which the average book on endocrinology is filled. This book may be classified as one entirely safe to put in the hands of the thoughtful endocrinologist, but not the more visionary one. Mechanically the book is beautifully presented, and the work of the editor is entirely creditable on the whole, though more careful editorial supervision is decidedly indicated. There is a considerable amount of editorial addenda which would increase the value of the work, particularly

as it concerns chiefly reports of cases and studies in the United States, were it more critically selected and the worthless material deleted. Another minor criticism that might be made is that the references follow no one system and are at times so incomplete, as to be valueless. M.

GYNECOLOGY. By WILLIAM P. GRAVES, M.D., Professor of Gynecology at Harvard Medical School. Third edition. Pp. 936; 534 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

WHEN the present reviewer had the pleasure of reviewing the first edition of this work he termed it a master work and predicted that it would enjoy unusual popularity. It is gratifying therefore to see that prophecy fulfilled, as evidenced by the appearance of the third edition, which even surpasses the high standards which were set by the preceding editions. Needless to say, the author has brought the text up to date; in fact, by the inclusion in detail of Sampson's recent work on "chocolate" cysts of the ovary, it is practically brought up to the minute. The radiation treatment of uterine cancer is fully discussed, the author definitely stating that the percentage of cancer of the cervix that he operates upon is constantly decreasing in favor of radiation. He also advises against operation *after* radiation of cervical cancers, reversing his opinion as expressed in preceding editions. Aside from a few more typographical errors than should be expected, we feel justified in continuing to refer to this book as a master work. B.

HEART RECORDS, THEIR INTERPRETATION AND PREPARATION. By S. CALVIN SMITH, M.S., M.D. Pp. 313; 128 illustrations. Philadelphia: F. A. Davis Company, 1923.

THE major portion of the book deals with electrocardiography, the smaller portion being devoted to polyography. In respect to illustrations this work stands out among the other books on this subject which have recently appeared. The electrocardiograms, which are reproduced numerous, are as beautiful and technically perfect as the reviewer has yet seen. This feature, together with the fact that most of the abnormal electrocardiograms are accompanied by normal tracings for purposes of comparison, and the clarity of the accompanying legends and text, renders the book an admirable one for the student or practitioner who desires to master the fundamentals of electrocardiography. A.

A TEXT-BOOK OF THERAPEUTICS. By A. A. STEVENS, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania. Sixth edition. Pp. 793. Philadelphia and London: W. B. Saunders Company, 1923.

DURING the fourteen years which have elapsed since the appearance of the fifth edition of this well-known work many advances have been made in pharmacology and therapeutics. Of the newer drugs which have come into general use, twenty-five are referred in the present edition, among them being thyroxin, mercurochrome, thromboplastin and quinidine. The articles on standard drugs have been brought up-to-date and in many cases considerably lengthened. As in previous editions, so here the presentation of numerous prescriptions is a feature of the work. A.

THE EXAMINATION OF PATIENTS. By NELLIS B. FOSTER, M.D., Associate Physician to the New York Hospital; Associate Professor of Medicine at Cornell University College of Medicine. Pp. 253; 67 illustrations. Philadelphia: W. B. Saunders Company, 1923.

THE writer in his preface remarks that the book has been written in the belief it will help practitioners of medicine, believing, as he does, that entirely too much attention is being paid to the development of laboratory methods and that entirely too much reliance is being placed upon laboratory examinations by the average practitioner. For this reason he thinks it is necessary to recall the fact that diagnosis depends not only upon laboratory studies but, what is much more important, upon correct physical examination by the use of the sense of touch, of sight and of hearing. With this idea in mind, the author proceeds to sketch in a simple, almost elementary manner, the examination which is required for a thorough study of a patient. The statements are clear, at times almost dogmatic; but this accentuated clearness and dogmatism adds much to the work, because the examinations are so very skilfully outlined by the author that the veritable tyro may receive thoroughly understandable information about going over a patient. One section the reviewer is particularly pleased with, namely, the section on neurological examination. This is a portion of examination which the average internist slurs over or, if he is on a hospital staff, is perfectly content to leave to the neurologist, whereas neurology is simply a branch of internal medicine and should be familiar to the internist—at least the first principles. It might be added that the author is entirely too modest in his statement that the book will help practitioners of

medicine. It can truthfully be said that it will help to train practitioners of medicine, as it should be particularly valuable to the medical student when he is first starting to learn methods of examining and handling patients. M.

THE TONSILS, FAUCIAL, LINGUAL AND PHARYNGEAL, WITH SOME ACCOUNT OF THE POSTERIOR AND LATERAL PHARYNGEAL NODULES. By HARRY A. BARNES, M.D., Instructor in Laryngology, Harvard Medical School; Laryngologist, Massachusetts Charitable Eye and Ear Infirmary; Laryngologist, Massachusetts General Hospital. Second edition. Pp. 217; 45 illustrations. St. Louis: C. V. Mosby Company, 1923.

WE are glad to notice another edition of the writer's work on the tonsils. This book we believe to be as complete and reliable a treatise on the tonsillar tissues as any publication we know of. It covers not only the anatomy, physiology and disease of the tonsils, but goes into considerable detail of the various surgical procedures. In this edition, besides the bringing of the whole subject up-to-date, there has been added a chapter on radiation, and the chapter on focal infections has been practically rewritten. The embryology and anatomy of the tonsil and the pathology and bacteriology of its various diseases are really the outstanding features of this work, and it is the excellence of this part of the book that makes it a valuable addition to every specialist's library. W.

INTERNATIONAL CLINICS. 33d Series, Volume III. Pp. 312. Philadelphia: J. B. Lippincott Company, 1923.

THIS number of *International Clinics* contains eleven articles on diagnosis and treatment of various disorders from allergic disease to disease of the nose and throat, and includes one on cancer, which is such a dangerous and revolutionary article that it should be deleted from a book which maintains the high characteristics of this publication. There are also six interesting contributions on pediatrics and half a dozen other clinics of the various phases of medicine and surgery. M.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Statistical Study of Tuberculosis Mortality.—SEWALL (*Am. Rev. Tuberc.*, 1923, 7, 445) heads a committee representing the Denver Sanitarium Association. With a grant from the National Research Council he has made a study of the tuberculosis problem in the State of Colorado. This study was made primarily to determine the ratio of deaths from tuberculosis developed in Colorado and the whole number of deaths from tuberculosis in the State. During the period from 1908 to 1920 a total of 23,608 deaths from tuberculosis is recorded in Colorado. Deaths of patients with tuberculosis which developed outside the State numbered 17,080, whereas deaths of patients with tuberculosis which developed while the individual was in the State numbered 3484, while there were 3044 deaths in patients developed in places unknown. This makes a ratio of those developed outside and in the State of 83.1 to 16.9. Analyzing these statistics, the writer calls attention to the fact that more than 40 per cent of the deaths from tuberculosis occurring each year in Colorado are in individuals who have lived in the State less than a year and that 50 per cent of them occur within the first three months of residence. These data are of particular importance because of the fact that they show that many of the tuberculous individuals are sent from their homes in a most hopeless physical condition. Added to this is the factor that frequently they are without pecuniary resources, which makes it impossible for them to find the right kind of care. Furthermore, and what is most important, is the fact that an excessive proportion of the tuberculous male sex that come to Colorado die, due in part to over-exercise combined with worry in individuals who do not allow themselves a period of rest for acclimatization. This study is very direct

A Fundamental Factor in the Recurrence of Inguinal Hernia.—SEELIG and CHOUKE (*Arch. Surg.*, 1923, 7, 553) say that the modern operation for herniorrhaphy dates from 1889 and 1890, when Halstead and Bassini published their studies. The fundamental principles underlying the permanent operative cure of hernia are: High ligation of the sac, adequate reinforcement of the defective abdominal wall, and primary wound healing. Despite these simple measures, the percentage of postoperative recurrences is far from encouraging. Unfortunately, there exists a disconcerting divergence of opinion regarding the frequency of recurrence varying from 0.8 to 12 per cent. Normal muscle will not unite firmly with fascia or ligament. It is therefore a useless procedure to suture the abdominal muscles to Poupart's ligament in the hope of buttressing a weak or ruptured abdominal wall. Fascia, however, unites well with fascia and the weak abdominal wall should be strengthened by use of one of the methods of securing fascia to fascia approximation.

Acute Perforation of Duodenal Ulcer.—SHAWAN and VALE (*Ann. Surg.*, 1923, 78, 342) states that perforation of the duodenum, whether simple or as a sequence to chronic ulcer is a condition uniformly susceptible to cure by immediately instituted surgical means. Two types of duodenal ulcer may perforate—the large, calloused, chronic variety, and the small soft, recent type. A positive history of previous ulcer will aid in diagnosing the former, while the findings of acute rupture are usually, but not always, the inaugurating symptoms in the latter. The early symptoms of rupture are fairly uniform, and are the typical findings in upper intra-abdominal hollow viscus perforation. However, pain, rigidity and restlessness may occasionally be intermittent, rather than constant; soft ulcers exhibiting more frequently the intermittent factor than do hard ulcers. History alone may indicate the perforating organ or may be of doubtful nature. Immediate closure of the perforation is the prime essential in the surgical treatment. The desirability of additional procedures depends on the local findings, and on the general condition of the patient at the time. Excision of the ulcer, modified pyloroplasty, gastro-enterostomy, and their combination, each has its indication. More extensive surgery is rarely advisable.

Traumatic Intestinal Rupture.—GRANT (*Lancet*, 1923, 205, 640) says that intestinal rupture without penetration of the abdominal wall sometimes referred to as a subcutaneous rupture is not an accident of common occurrence. The majority of ruptures clearly occur in the small intestine and the comparative immunity of the stomach, duodenum and colon is striking. Regarding rupture of the small intestine, the jejunum was more commonly injured than the ileum, and of the 74 jejunal lesions, 7 were found within 18 inches of the duodeno-jejunal junction, an occurrence which cannot be explained by chance. It is certainly very suggestive that it is the second or third loop of the jejunum which is commonly injured at the point at which it crosses the vertebral column. The complication of injury to the mesentery is found, according to Moynihan, in 10 per cent of cases. In most cases it does

not appear to influence the prognosis except when the mesentery is torn from the bowel along its line of attachment. This condition called mesenteric disinsertion has the immediate consequence of hemorrhage and the remote consequence of gangrene. The mortality in this series was enormous, 78 per cent, and there can be little doubt that early exploration of the abdomen would reduce this to a considerable extent.

THERAPEUTICS

UNDER THE CHARGE OF
SAMUEL W. LAMBERT, M.D.,
NEW YORK.

Concerning Sulfoxylsalvarsan.—GALEWSKY (*Deutsch. med. Wchnschr.*, 1923, 22, 712) tried out a preparation of sulfoxylsalvarsan. He used this preparation for the treatment of syphilis in a series of 500 patients, to whom he gave 4000 injections. He claims that although the reaction is very much slower than with ordinary salvarsan and the lesions respond more slowly, it is excreted much more slowly and therefore has a more desirable effect. He claims that the cure is more permanent with this solution than with straight salvarsan and that reactions are very uncommon. He starts with 2 cc of a 10 per cent solution or 4 cc of a 5 per cent solution and increases it to as high as 6 cc of a 10 per cent solution. Four to 10 injections are given, depending on the severity of the case, at eight-day intervals. In late syphilis where large doses are given the interval between injections should be ten to twelve days because of its slow excretion.

Treatment of Hay Fever with Optochin Hydrochloride.—HAIKE (*Deutsch. med. Wchnschr.*, 1923, 22, 711) uses optochin hydrochloride for the treatment of hay fever both prophylactically and during the attack if necessary. The preparation he uses is: Optochin HCl (not basic), 0.25; glycerin pur., 2; aqua dest., 25. The treatment is started about one month before the attack is expected and is given two or three times a week. The nasal mucosa is first anesthetized with cocaine and then the solution is applied locally.

The Role of Anoxemia in the Causation of Tetany during Hyperpnea.—For the study of the role of anoxemia in tetany of hyperpnea two methods were employed by GRANT (*Am. Jour. Physiol.*, 1923, 66, 274). The first was the determination of the oxygen consumption of the entire body, as shown by an analysis of the respiratory exchange, and the second was the determination of the utilization of the oxygen from the blood, as indicated by venous oxygen unsaturation. During the alkalosis and tetany of hyperpnea there is a greater

consumption of oxygen by the entire body (as determined by a study of the respiratory exchange) than in a similar hyperpnea unaccompanied by alkalosis and tetany. The oxygen unsaturation of the venous blood from the arm was greater during hyperpnea with tetany than with hyperpnea alone. Hyperpnea with alkalosis and tetany was accompanied by an increase in the oxygen saturation of the arterial blood. Inhalations of pure oxygen had no effect on the development of symptoms of tetany during hyperpnea, and hyperpnea with a mixture of equal parts of oxygen and air resulted in tetany in the same manner as though air alone had been used. The author is therefore forced to conclude that anoxemia plays no part in the causation of tetany during hyperpnea and that the lowering of the carbon-dioxide content of the blood under these conditions is not sufficient to cause a tissue asphyxia.

The Treatment of Chronic Malaria. — The method of treating chronic malaria advocated by DIXSON (*Brit. Med. Jour.*, June, 1923, p. 1087) is the more or less continuous coincident administration of an aperient with the quinine. A small dose of calomel (1 grain) is given at once and repeated in an hour or so; this single dose is administered each night at bedtime. This is followed next morning by a saline aperient. This continuous administration of calomel in doses too small to cause mercurialism is, in his opinion, essentially important. The quinine is given in 3- or 4-grain doses in the form of the hydrochloride, and is administered an hour before meals and at bedtime to ensure rapid absorption. This treatment is continued for two months. Dixson says that by this method he has never failed to rapidly relieve urgent symptoms; there is generally no attack or only a slight one during the first week of treatment and none afterward. The few cases followed for a year or more after treatment have been free from attacks, although he does not claim these cases as cured. The advantages of the method are that it is not unpleasant, is simple and easily carried out, the result is produced more rapidly than by ordinary routine and there is no risk of permanent disorders of the nerves due to quinine.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Puncture of the Cisterna Magna. — AYER (*Jour. Am. Med. Assn.*, 1923, 81, 358) feels that cistern puncture, when carefully performed, has proved safe in a great many instances. Repeated punctures for the introduction of serum may be safely made. Indications for cistern puncture in the order of importance, are: In the treatment of meningococcic meningitis block; in the serum treatment of cerebral syphilis;

in the early diagnosis of compression of the spinal cord; for obtaining cerebrospinal fluid for examination when elsewhere impossible or inadvisable; as one point of entrance to the subarachnoid space for the purpose of irrigation. The tapping of the cistern in infants differs from that in the adult. It is best to start at the base of the neck and direct the needle upward and slightly forward, inserting it gradually until the occipital bone is reached, and then working it forward gradually until it slips into the foramen magnum. While the depth at which the cistern is reached must vary with the individual, it has been found to be less variable than in lumbar puncture. In adults the distance from the skin is seldom less than 4 cm., and usually less than 5 cm. Rarely is the distance greater than 6.5 cm. In any condition in which the cisterna magna is likely to be obliterated either by pressure or by adhesions, or in which the cistern may be displaced, the procedure must be considered as contraindicated. In that such conditions would usually lead to early increase of intracranial pressure, the most reliable guide would be choked disk. In the presence of papilledema or choked disk, cistern puncture should not be undertaken. Without a knowledge of the anatomy of the subarachnoid spaces and an appreciation of the physiology of the cerebrospinal fluid, and without previous experience on the cadaver, cistern puncture should not be undertaken.

Tuberculous Osteoarthritis in Infants.—**BROCA** (*Nourrisson*, 1923, 11, 81) did not find tuberculous osteoarthritis frequently before the age of six to eight months. Diagnosis of the resulting pseudoparalysis is easy when located in articulations accessible to palpation. The child does not move the limb, and cries if it is lifted; local pressure will show that the tender point is close to the epiphysis. With signs of rachitis in a child fed from the bottle with over-sterilized milk, specific treatment for scurvy should be tried, even if the gums are normal. If the pain is located in the upper femur or in the spine, diagnosis is more difficult, but restricted movements of the hip, and curving of the spine suggest a tuberculosis lesion. The roentgenograms of two children of this series showed an opaque line, probably from extravasated blood, at the junction of the shaft, of the femur and the epiphyseal cartilage. This was accepted as differentiating scurvy from rachitis. The author always suspects scurvy with pain in the limbs. He has seen children near to death, cured in a few days by lemon juice, after several physicians had given the diagnosis of Pott's disease. The spine was stiff and curved, but the pain was manifested only when the limbs were touched. He believes that Pott's disease is rare in infants, and that it is frequently confused with rachitic curvature of the spine. When the seated child stoops with a general curve of the back which quickly disappears when placed prone, and lordosis appears in the dorso-lumbar region when the feet are raised Pott's disease may, as a rule, be excluded. One infant of sixteen months showed dorso-lumbar kyphosis when sitting on its mother's lap, but when placed on its abdomen a slight hump persisted at the lower dorsal vertebræ. The prognosis is unfavorable as in all surgical tuberculosis in infancy. Laxity of joints and muscular weakness in infants with rickets facilitates sprains which are frequently misinterpreted in the hip joint although they may be easily diagnosed in superficial joints. In the presence of suppuration death always follows.

Biological Food Tests: Vitamine A in Skimmed Milk.—MORGAN (*Am. Jour. Physiol.*, 1923, 64, 538) shows that although dried skim milk, and presumably fresh skim milk as well, is not altogether lacking in vitamine A, it is impossible to obtain normal growth over a prolonged period by the use of this substance alone. An immediate and striking improvement was noted in most of the animals given the skim milk after decline from vitamine-A deficiency. This was followed at varying intervals by an equally rapid decline, ending in death if the treatment was continued. Successful growth on a diet containing both the skim milk and small amounts of butter fat indicated that the eventual failure on the skim-milk diet was probably not due to the presence of toxic or inhibiting substances in the skimmed milk. Quantities as large as 5 gm. of the dried skim milk were found to be less effective than 0.25 gm. of butter fat of the same origin. The proportion of vitamine A in dried skim milk and butter fat would appear to be less than 1 to 20, in fresh skim milk and butter fat less than 1 to 100 and average whole milk should be more than eight times as valuable as a source of vitamine A than the skim milk from it.

Intracutaneous Reactions in Pertussis.—HULL and NAUSS (*Jour. Am. Med. Assn.*, 1923, 80, 1840) used nine different preparations and made 341 intracutaneous injections. This work was done at an institution housing about 2000 patients, at which an epidemic of whooping-cough was at the time developing. The ages of the children tested were from eight to twelve years. Preparation A consisted of freshly grown strains of pertussis bacilli containing both of Krumweide's serological types. The preparation was killed by heat at 60° C. for one hour and preserved with 0.1 per cent tricresol. The dosage was 0.5 minim. Preparation B was likewise a freshly prepared product, being but three weeks old. It contained seven strains of pertussis bacilli, killed by heating at 53° C. for thirty minutes, and preserved with 0.5 per cent tricresol. The strength was 2,000,000,000 organisms per 1 cc and the dosage was 1 minim. With these two preparations in most instances the reactions were strongest at the end of five hours, decreasing slightly in twenty-four hours and rapidly disappearing in forty-eight hours. There was no uniformity of results. Nearly all the children showed positive reactions, but some of the whooping-cough cases were negative. Preparation C consisted of freshly grown pertussis bacilli killed by the use of chemicals, no heat being employed. The dosage was 1 minim, containing 3,000,000,000 organisms per 1 cc. As a control, Preparation D was obtained from the same manufacturers, consisting of influenza bacilli prepared after the same manner. As a rule the C pertussis material gave a distinct reaction in five hours, continuing for twenty-four hours, but much lessened in forty-eight hours. The D influenzal material gave its strongest reaction in five hours, disappearing in most instances in twenty-four hours. It was noted that only one individual was negative with the D material. Two more preparations were used, consisting of vaccines that had been killed by heat and allowed to stand for a considerable period and autolyze. The first preparation, E, consisted of a single strain, the pertussis bacillus killed by heating for one hour at 60° C. and preserved with 0.1 per cent tricresol. It was more than a year old when

used. The second, F, contained five strains of pertussis bacilli killed by heating at 54° C. for thirty minutes and preserved with 0.4 per cent tricresol. It was three years' old when used. With these preparations all of the bronchitis cases were negative. In order to determine what factor in pertussis vaccine was responsible for the skin reaction, some of preparation F was heated at 100° C. for thirty-five minutes to make preparation G. The results indicated that no thermolabile material in the product was found so far as the skin reaction was concerned. Some of the original material was then centrifugated at high speed to clear it of organisms, and the supernatant fluid, which was in reality an autolysate of pertussis bacilli, was injected as preparation H. The results were the same as with the inactivated whole vaccine G. Some of this autolysate was then inactivated by heating at 100° C. for twenty minutes and centrifugated at high speed to throw down any precipitate. This made preparation I. Of the few patients who received this vaccine all reacted. It seems apparent that whatever substance in the vaccine is responsible for the skin reaction it was in solution and was not destroyed by heat. As a result of these investigations the authors do not feel that preparation of pertussis bacilli can be used intracutaneously to diagnose whooping-cough.

Studies on the Therapeutic Application of Bacillus Acidophilus Milk.—CHEPLIN, FULMER and BARNEY (*Jour. Am. Med. Assn.*, 1923, 80, 1896) feel confident that viable cultures of *B. acidophilus*, when ingested in sufficient amounts, can be successfully implanted in the human intestine, and that the resultant intestinal flora can be maintained as long as the administration of the culture continues. As far as is now known *B. acidophilus* does not elaborate toxic or other injurious by-products. Its therapeutic virtue is embodied not only in its ability to suppress *B. coli* but also to its inhibiting influence on other toxigenic intestinal microorganisms. *B. acidophilus* milk therapy possesses distinct merits in the treatment of chronic constipation and mucous colitis. Its beneficial effects in simplifying the complex fecal flora are manifested in two well-defined ways. In the constipation group the physical characteristics of the feces are noticeably changed, becoming yellowish, soft and comparatively odorless, quite resembling the infantile type of stool, and accompanied by the elimination of pain at straining at stool. In the diarrhea and mucous colitis group there is a gradual formation of the fecal material, finally resulting in soft, light and partially formed stools with a complete disappearance of the mucus. There is marked improvement in the clinical picture by the relieving of the toxic symptoms. The accumulated evidence and clinical belief that the absorbed by-products of intestinal putrefaction are harmful strengthens the investigators' belief that the theory of autointoxication deserves more consideration than has heretofore been given it. *B. acidophilus* milk apparently reduces the complex intestinal flora and greatly reduces the elaboration of toxic by-products. In their experience the authors have not encountered a case of chronic constipation of no matter how long duration that did not respond to this treatment. Immediate results should not always be expected. In some cases in their series weeks were necessary before the improvement began.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Provocation of the Wassermann Reaction in the Spinal Fluid.—CESTAN, RISER and BONHOURE (*Ann. de dermat. et de syph.*, 1923, 4, 145) report the successful and repeated provocation of the Wassermann reaction and the colloidal-benzoin reaction in the spinal fluid by the intravenous administration of small doses of arsphenamine in patients with old neurosyphilis. Provocation of syphilitic reactions did not occur in any cases of non-syphilitic disease of the nervous system, although from one to five injections of 0.3 to 0.45 gm. neo-arsphenamine were used in the effort to obtain false provocative effects. No effect upon the albumin content or the lymphocyte count of most of the reactivated fluids was observed. In those patients who had entirely normal spinal fluids, but positive blood Wassermann reactions, no provocative effect on the spinal fluid was observed. The provocative effect may be delayed as late as ten days and is practically confined to those patients who have shown evidence of involvement of the nervous system in the past. It is estimated that at least 50 per cent of old cases of neurosyphilis will show these provocative reactions in the spinal fluid. Occasional increase in the lymphocyte count may be observed as part of the provocative effect.

Biological Reactions of Arsphenamine.—An important series of reports on the biological reactions of the arsphenamines includes the following: OLIVER and DOUGLAS (*Arch. Dermat. and Syph.*, 1923, 7, 573), OLIVER and DOUGLAS (*Ibid.*, 1923, 7, 778), OLIVER, YAMADA and KOLOS (*Ibid.*, 1923, 7, 1) and OLIVER, DOUGLAS and KOLOS (*Ibid.*, 1923, 8, 359). In this series of studies the authors find that arsphenamine has little if any action as an antithrombin in the production of incoagulability of the blood observed in fatal doses. The action is believed to be on the fibrinogen element of the coagulation complex, the fibrinogen and other globulins being rendered incoagulable to heat or thrombin. While the action is similar to that of an alkali, the action of an alkaline solution alone will not explain all the results obtained in the authors' experiments. The proteins involved are in no sense destroyed, for they can be precipitated by carbon dioxide along with the arsphenamine. In further studies it was found that the plasma protein, especially the globulins, form compounds with arsphenamine, both *in vitro* and *in vivo*. When arsphenamine is administered *in vivo* this union of the drug with the globulins protects the red cells from agglutination unless excessive doses are given, in which case reaction and death may occur from agglutination. The arsphenamine content of the various globulin-arsphenamine compounds varies with the hydrogen-ion concentration. Within certain

limits of H-ion concentration only traces of inorganic arsenic, such as sodium arsenate, are found. Other hydrophylic colloids in addition to the globulins, such as egg albumen and gum arabic, react in a similar way with arsphenamine. In the next series of studies the authors make practical application of this last-mentioned observation and found that the combination of arsphenamine with hydrophil colloids before injection decreased the toxicity of the injected drug, this being essentially an augmentation of the physiological protection against toxic action. Gelatin was found to be especially effective in this respect. The effect of the combination of arsphenamine with gelatin is to remove the physical toxicity of arsphenamine, no agglutination of red cells occurring. The chemical toxicity is reduced to three-fifths and the circulatory disturbances produced by its administration are markedly lessened. The series of studies is completed by observations in the therapeutic efficiency of gelatin arsphenamine and a comparison with the disodium arsphenamine which is usually administered. The authors find that gelatin arsphenamine, while somewhat less trypanocidal *in vitro* than disodium arsphenamine, is retained in the animal at a higher concentration for a longer period than is disodium arsphenamine, and is as effective as disodium arsphenamine in the treatment of experimental trypanosomiasis and rabbit syphilis. Under certain conditions it is more effective. Therapeutic indexes established on the basis of the late or chemical toxicity of the two preparations favor gelatin arsphenamine. The immediate toxic effects of disodium arsphenamine may be avoided under experimental conditions by the use of gelatin arsphenamine without any sacrifice of therapeutic efficiency.

Granuloma Inguinale.—GAGE (*Arch. Dermat. and Syph.*, 1923, 7, 303) summarizes the literature and reports cases of the much discussed entity of inguinal granuloma. He believes the causative organism to be the Donovan body found as an inclusion in the leukocytes. His directions for obtaining a satisfactory smear emphasize the value of squeezing lymph from a piece of tissue clipped from the active edge to avoid the dilution of the specimen by blood, as in smears from the secretion. Scrapings from the cleaned and dried ulcer base are also valuable. Wright's stain is satisfactory. Not every cell inclusion in an endothelial phagocyte is to be regarded as a Donovan body. The pathological process is that of a sclerosing granuloma. In treatment the author commends a 1 per cent solution of tartar emetic in distilled water, which can be sterilized by boiling, without the necessity of filtration through a Berkefeld filter. The initial dose is 2 cc diluted with 8 cc of distilled water and given intravenously, the injections being repeated every other day with 1 cc more of the tartar emetic solution. As high as 20 cc has been given by some authors. Brackish taste, dizziness, nausea and pains in the bones have been noted as complications, and in elderly patients care must be taken to watch for renal irritation. In patients with concomitant syphilis treatment for this disease may be of benefit, but in others it has little or no value. Surgery is given qualified commendation, especially cautery excision, provided the ulcer is accessible and can be completely removed with a wide margin. Relapse will occur if treatment is not continued for

several months after the lesions heal, and the patients should be kept under observation for at least a year. Improvement usually sets in promptly, and by the fifth injection most cases are healed. Local applications, unless of tartar emetic solution, are of little avail. Every genital ulceration with negative inguinal glands should be searched for evidence of granuloma inguinale. The disease is endemic in Louisiana and other southern states.

Wassermann Reaction in Leprosy.—Utilizing the large material of the National Leprosarium, KOLMER and DENNEY (*Arch. Dermat. and Syph.*, 1923, 8, 63) have tested the well-known conception of the production of false positive blood Wassermann reactions in leprosy against the results obtained by the use of the Kolmer technic. In a series of 159 cases of leprosy of various types 17 per cent of positive blood Wassermann reactions were obtained, but all of the Wassermann positive cases were said to present evidence of syphilis. With an old technic apparent false positives were obtained in an additional 7.2 per cent. The new Kolmer test, therefore, does not appear to yield false positive tests in leprosy. False positives seem to be especially the result of the use of alcoholic antigens saturated with cholesterol. Lepers presenting a positive Wassermann test with the Kolmer technic should therefore be treated for syphilis. YAGLE and KOLMER (*Arch. Dermat. and Syph.*, 1923, 8, 183) examined the serums of 28 lepers and came to the conclusion that the Kahn precipitation test likewise does not yield false positive results in non-syphilitic lepers.

Studies on Etiology of Pemphigus.—EBERSON (*Arch. Dermat. and Syph.*, 1923, 8, 204) reports the isolation from the blood of 7 patients with chronic pemphigus, 2 of the malignant type, of a strictly anaërobic, toxin-producing coccoid organism. Cross-agglutination was obtained, but the experiments in the reproduction of the disease in animals are not regarded as conclusive as yet.

Experimental Aspects of Iodide and Bromide Exanthems.—WILE (*Arch. Dermat. and Syph.*, 1923, 8, 410) discusses observations on the treatment of patients suffering with the mental symptoms and cutaneous lesions of bromism. He finds that the intravenous administration of decinormal salt solution in doses of 100 to 200 cc every two or three days has a marked beneficial effect on both. His first case was, however, thrown into a species of shock by the first injection. Bromine could not be demonstrated in the urine in any of the cases until after the first injection of salt solution.

Absorption of Gray Oil.—LEVY-BING, BELGODERE and AUCLAIR (*Ann. d. mal. ven.*, December, 1922, p. 887) find by roentgenographic examination of the sites of intramuscular injections of gray oil and of various bismuth salts that the mercury in gray oil is absorbed with extreme slowness, but that bismuth disappears comparatively rapidly from the tissues, and for that reason is the preferable medicament of the two in the treatment of syphilis. It will be recalled that Cole, of Cleveland, demonstrated the extreme slowness of the absorption of gray oil by the same method.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Blood Sugar during Pregnancy.—ROWLEY (*Am. Jour. Obst.*, 1923, 5, 23) has studied 53 patients during pregnancy to determine the condition of the blood as regards the presence of sugar. The child was also studied so far as possible in these cases. It was found that the average range for blood sugar concentration for normal pregnant women is 0.09 per cent to 0.11 per cent, which was the same as that found in the non-pregnant. In other words the average pregnant woman in good health has the same blood sugar concentration as has the non-pregnant patient. In the 53 cases studied the average of blood sugar was 0.11 per cent. In 32 cases fetal blood was taken from the umbilical cord immediately after delivery, and the blood sugar content was studied. This was found to be 0.09 per cent. On the second day after the birth of the child in 22 women the blood sugar concentration was 0.14 per cent. The interchange of glucose through the placenta undoubtedly depends on the higher concentration of blood sugar in the mother. It has been thought that the muscular exertion of labor had something to do with hyperglycemia found after labor, but the writer believes that such is not the case. Anesthesia with ether is a contributing but not a determining factor in producing a rise in the sugar concentration of the blood in the umbilical cord. Asphyxia produces a more marked rise than does anesthesia with ether. So far as postpartum hyperglycemia is concerned, involution of the uterus is not a primary factor; but on the other hand it is probably true that the general physiological changes associated with the uterus have a considerable influence in producing postpartum hyperglycemia. It has long been recognized that there are certain types of toxemia in which there is an increase in the blood sugar concentration.

Sugar in the Urine during Pregnancy.—WELZ and VAN NEST (*Am. Jour. Obst.*, 1923, 5, 33) have studied the question of sugar in the urine of pregnant women to determine a reliable test, and also to use this test in the diagnosis of early pregnancy. The method employed was to have the patient report to the clinic in the morning without breakfast, the urine taken by catheter, and if normal, the test continued and a specimen of blood taken for blood chemistry; then 150 grams of glucose dissolved in 500 cc of tea was given, and the patient was required to keep the prone position for forty-five minutes; this to avoid vomiting. The urine was taken by catheter forty-five minutes after the sugar was administered and the urine was examined for sugar. It was again taken at one hour and at one and a half hour periods and examined. Immediately after finding sugar in the urine another blood specimen was taken and blood sugar was estimated. The blood for the

second sugar test is usually taken between the one hour and the one and a half hour periods. From this study the writers believe that a spontaneous artificially induced renal glycosuria with a blood sugar estimation below 0.19 per cent in the first twelve weeks after conception is a valuable aid in the diagnosis of early pregnancy. In the cases which they studied the test was correct in more than 95 per cent.

Blood Studies in Normal Pregnancy.—DREBS and BRIGGS (*Am. Jour. Obst.*, 1923, 5, 67) review to a considerable extent the studies of blood in normal pregnancy. They add to this review tables giving the age of the patient, whether primipara or multipara, period of gestation and the presence or absence of albumin and sugar in the urine. The blood-pressure is also charted and then the non-protein nitrogen, urea, uric acid, creatinine, sugar, sodium, potassium, calcium, magnesium, phosphorus and sodium chloride of the blood. The results of the study of the blood with special reference to the inorganic constituents shows a great constancy of all the elements in normal pregnancy, regardless of the period of gestation. To this, however, there is one important exception, that during the last weeks of pregnancy the quantity of calcium is slightly decreased. This arises from the demands made by the fetus and also the establishment of lactation. The table is an interesting and valuable one, and the paper concisely stated is excellent for reference.

The Bacteriology of Fatal Infection Following Abortion.—This familiar subject receives a contribution from MOODY (*Am. Jour. Obst.*, January, 1923, p. 78). Twenty-eight cases were studied. Cultures of the blood were taken from the heart, peritoneal, pleural, pericardial and cerebrospinal fluids, the pulp of the spleen and the contents of the uterus. In addition stained direct smears were also made. Other methods of inoculation of culture material were employed. It is interesting to note that cultures during life were made from the blood of 5 of these patients. In only 1 were any organisms found. These were beta-streptococci, and in this case there was septic endocarditis. Reviewing the results obtained, it is found that in 24 of the 28 cases some one organism appeared in several of the fluids from the body. The prevailing organism was the beta-streptococcus which is hemolytic. The results produced were peritonitis or thrombophlebitis. These processes were in varying locations, different degrees and different sequences. These two results were rarely combined, but a difference in the bacteriology to correspond to the two types of alterations could not be definitely established. In 13 of the 28 patients it was admitted that the pregnancy had been interrupted artificially and purposely. There were various lesions in these cases but as a rule the various forms of bacteria were abundantly present. Two patients stated that no interference had been practised, but they had taken pills and used douches. Both had been ill about three weeks with cramps, chills and fever. They had gangrenous endometritis and other septic lesions. The beta-streptococci were found in these cases. Another patient had been attended by a midwife and doctor, but developed chills, fever, sweats and swelling of the left leg with beginning gangrene. After

death an abscess was found in the wall of the uterus with thrombosis of the pelvic veins. Staphylococci and *B. coli communis* were found in the blood and the heart and inferior vena cava; there were no organisms in the peritoneal fluid. In these cases the hemolytic streptococcus was more often present than any other organisms, but *B. coli* and staphylococci were often found. Apparently some outside influence, such as the use of instruments, douches or other agents, is necessary to produce a generalized infection.

Metabolism Readings in Eighty-four Pregnant Cases.—CORNELL (*Surg., Gynec. and Obst.*, 1923, 36, 53) made metabolism readings in 84 pregnant cases and found the metabolic rate increased. It was impossible to find an average, as there is wide variation, and many factors tend to make these results unreliable. One is the unstable mental and nervous condition of these patients. With some the very making of the test produces hysterical excitement which destroys the result. Even where pregnant women were evidently toxic, there was such variation in the results as to make them unreliable. No accurate information could be obtained as to the degree of toxicity or the recovery in a given case, nor in any case could it be said that labor should or should not be induced. There was no way from this test of predicting the death of the fetus. It was found that very considerable time, effort, expense and patience were required to carry out the test, and it was thought that this was far out of proportion to the value of the information so obtained.

Pyelitis in the Newborn.—RUNGE (*Zentralbl. f. Gynäkol.*, 1923, No. 8, 319) reports the case of a vigorous male infant, breast fed, ten days old, mother and three sisters normal, pregnancy and birth normal and without complications, that was suddenly deprived of breast milk and given artificial feeding, cow's milk, diluted one-half and sweetened, followed on the next day by high fever. The umbilicus was clean and the umbilical cord separated on the eighth day without lesions. There was no evidence of infection of the intestines. Examination of the urine showed abundant leukocytes and colon bacillus in pure culture. The child was ill for twelve days but gradually grew better as a wet-nurse was secured for it and it was given the treatment usually employed. From the third to the tenth day of the disease the child had intense jaundice with the presence of bilirubin in the urine, although urobilin and urobilinogen were absent. The child had been without fever for three days when a second attack of fever developed followed five days later by death. Just before death symptoms of bronchopneumonia developed. Autopsy showed several bilateral pyelitic infarcts, small abscesses in the kidney substances, dilatation of the pelvis and ureters and a mild cystitis, but the urinary tract remaining pervious. In the right kidney vein there was a firm thrombosis. Both pulmonary arteries were closed by embolic material and there were hemorrhagic infarcts in the lung. In the pelvis of the kidneys there was moderate swelling and redness of the mucous membrane. Apparently the bacilli found their way into the body from the cow's milk given to the child.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Choice of Treatment in Cancer of the Cervix.—In 1920 GRAVES (*Boston Med. and Surg. Jour.*, 1923, 188, 1006) reported that his operability rate for cases of cancer of the cervix was 64 per cent. Since that time, as a result of the increasing reliance on the use of radium, the percentage has appreciably dropped. In dealing on the operative treatment of a given case, Graves states that the question is no longer, "Can we perform a radical operation without killing the patient," but rather, "Have we, by performing a radical operation, a reasonable chance of *curing* the patient?" It is unnecessary to state that he believes emphatically in operating on curable cases. Furthermore, his experience with radium leads him to believe that, in the absence of metastasis, a case of cervical cancer that is curable by operation is also curable by radium, but he prefers to operate upon the operable cases for the following reasons: (1) Although cancer of the cervix, as a rule, metastasizes in the regional lymph glands comparatively late in the disease, nevertheless it not infrequently happens that in cases where the local affection is early and the growth frankly operable the glands are found involved, especially in young women. Such cases may sometimes be cured by operation, whereas if radium be used the disease localized in the cervix may be cured, but the more distant regional lymph nodes cannot be reliably treated even by the most powerful internal and external radiation. (2) In curable cases with the disease definitely localized in the cervix there is no doubt that surgical removal of the entire organ is a more certain means of eradicating the growth than is radiation. Everyone who has used radium has been chagrined, on occasions, to find that he has missed the mark and that only a part of the growth has been successfully stormed by his radium forces. (3) The proper relationship of the dosage to the individual is an unknown but probably important factor. Moreover, cancer of the cervix represents in its category several different types of carcinoma which possess individual characteristics of growth, and which doubtless react differently to radium. Many operators make a preliminary application of radium, some with the purpose of making an inoperable case operable, others using it as a routine prophylaxis in a frankly operable case. Graves considers such a procedure very unsatisfactory, as the increased difficulty of operation, septic complications of convalescence and invariable recurrence of the disease are his experiences under such conditions. He sees no justification

for the popular preoperative radiation as a routine, as it cannot reach farther than the knife while it has the disadvantage of devitalizing the normal tissues and making them more susceptible to sepsis when the operation is performed. In regard to postoperative radiation, Graves employs it only when there is a doubt as to the completeness of removal of the cancerous tissue, and in such cases radium is applied as soon as the vaginal wound is healed. In some of these cases radium has undoubtedly prolonged the patient's life and increased her comfort, and on that account has influenced Graves' judgment during the progress of an operation in cases in which the disease is found to be more extensive than was expected. Thus if the parametrium proves very difficult, he abandons the complete Wertheim technic and takes a short cut on one or both sides to the cervix, relying on later radium treatment to take care of possibly diseased parametrial tissue which could not be removed without considerable danger to the patient.

Chronic Urethritis in Women.—The symptom-complex occurring in women and characterized by frequent and painful urination is found so often to bear no apparent relation to bladder or kidney lesions that its study has been undertaken by COTE and SMITH (*Boston Med. and Surg. Jour.*, 1923, 188, 596) to determine, if possible, to what extent chronic urethritis may be responsible. By chronic urethritis they refer to a low-grade inflammatory process in the urethra, the pathology of which is probably similar to that found in chronic urethritis in the male. In other words, there are areas of submucous round-cell infiltration and round-cell invasion of the tissues about those urethral glands which occur in the female urethra as well as in the male. This condition is, of course, a minor ailment, never directly affecting the health of the individual, yet from the point of view of comfort and happiness, chronic urethritis ranks much higher than many more serious diseases. The condition is frequently diagnosed as cystitis, irritable bladder or trigonitis. In typical cases the correct diagnosis can be made by the simple maneuver of passing a catheter, securing a specimen of urine and dilating the bladder. If the urine is clear and shows only an occasional leukocyte, true cystitis can be excluded. Of the 50 cases which the writers studied, cystoscopy was performed in 78 per cent. In 62 per cent of these the trigone showed a variable pathology. Some showed bullous edema; in others there was congestion, the bloodvessels dilated and tortuous in the trigonal region, but the bladder walls showing no pathology. The commonest symptoms were: (1) Frequency of urination, and (2) pain in or about the bladder. The treatment used consisted of dilatation of the urethra followed by instillations of 15 per cent solution of argyrol. After determining the urethral caliber in each case the dilatation was accomplished by gradually increasing the size of the dilator at each visit, being careful not to dilate too rapidly or too forcefully. In 20 per cent of the cases this treatment sufficed to give complete relief. In the remaining cases, after catheterization of the bladder, with the patient in the knee-chest position, an endoscope, as large as the urethra permitted, was introduced past the internal urethral orifice and 20 per cent silver nitrate solution was applied to the entire length of the urethra as the endoscope was withdrawn. The

reaction to this treatment varies in direct proportion to the degree of inflammation present, the dysuria and frequency are often increased for one or two days, but marked improvement usually occurs after the second or third treatment. In practically every case a clinical cure was obtained, but in following such cases over a period of years one is impressed by the likelihood of recurrence of the symptoms whenever the patient catches cold, becomes overtired or otherwise feels below normal. Recurrent attacks, however, usually clear up more rapidly than does the original attack. This condition is probably caused in the great majority of cases by antecedent infection, either urogenous or gonorrheal. Infections in the tonsils and pathological conditions in the pelvis do not appear to be frequent causative factors.

Late Ectopic Gestation.—In connection with their report of two cases of ectopic gestation near term, HAYD and POTTER (*Am. Jour. Obst. and Gynec.*, 1923, 5, 601) state that the crux of the whole problem is what shall be done with the placenta, but they are satisfied that there are no hard-and-fast rules to govern the surgeon. They believe that the best surgeons today let it alone, *in situ*, if the sac cannot be adequately clamped off and the whole mass removed. If it sloughs it is treated as any other sloughing wound in which suppuration and sepsis occurs. Of course, these are most undesirable complications, but they give a better outlook for ultimate recovery than the tearing away of a placenta from its firm bed of attachments with a resulting primary fatal hemorrhage. As a result of their experience and study of this subject they have come to some definite conclusions which may be well for us to review. They believe that the diagnosis of extra-uterine pregnancy at term should be made and vaginal examination reveals the most important sign, namely, a cervix, although soft, has not the characteristics of a cervix at term with an intra-uterine product, and above it can be felt a hard body which is the uterus, perhaps pushed to one side. A history of bowel obstruction is of great importance. Extra-uterine fetation always calls for surgical relief and the operation should be undertaken just as soon as the diagnosis is made, whether the embryo is viable or not. If, however, the case has passed beyond the seventh month the surgeon may wait until the baby is stronger, providing the patient is in good condition, can be seen often and kept under the closest observation. We should not allow the woman to go into spurious labor and wait for the death of the baby to take place with the transformation into adipocere, because such a course could only help in the delivery of the placenta, the sac would probably be just as adherent to the surrounding structures, and if attempts were made to separate it a fatal hemorrhage might take place. If the mass can be tied off at both ends an attempt should be made to remove the sac and placenta, which will perhaps be possible if the pregnancy be tubal or tuboövarian; but if there be much oozing or bleeding the sac should be packed with 5 per cent iodoform gauze and the placenta be left *in situ*, or the sac can be sewed to the abdominal wall, where very great caution must be exercised not to disturb the placenta by pulling or tugging on it until it is free in the sac cavity.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Invasion of the Body by Bacteria from the Intestinal Tract.—Desiring to know to what extent, under what circumstances and by what route organisms within the intestine may pass through the wall and enter the blood stream, MOODY and IRONS (*Jour. Infect. Dis.*, 1923, 32, 226) conducted 7 experiments on 23 dogs. After isolating the thoracic duct under anesthesia, the animals were fed suspensions of *B. prodigiosus*, *B. pyocyaneus* or *Streptococcus hemolyticus*, and cultures from the thoracic lymph at intervals of five to ten minutes for from one to three hours and from portal blood and viscera after death were made on blood-agar and plain-agar plates and dextrose bouillon. The bacteria which were introduced by the stomach tube could not be recovered from the chyle, blood or organs. When the organisms were injected into the duodenum by needle puncture in 1 of 6 dogs *B. pyocyaneus* was recovered from the thoracic duct eighty and one hundred and five minutes after injection, and similarly *B. prodigiosus* was recovered ten and sixty-five minutes after inoculation in 1 of 2 dogs. In these experiments leakage from the puncture and resulting direct passage of organisms from the peritoneum by way of the lymphatics to the thoracic duct could not be excluded. The authors believe that "under conditions in which resistance to infection is decreased, or when unusually hardy organisms enter the bowel, or when lesions of the bowel are present, it is reasonable to suppose that bacteria may enter the blood stream from this source."

The Experimental Production of Gall Stones in Dogs, in the Absence of Infection, Stasis and the Gall-bladder Influence upon the Bile.—"Numerous circumstances and influences which favor the development of gall stones are now recognized, but uncertainty exists as to which of them are contributory in character and which critical, and as to whether, indeed, the decisive causes for cholelithiasis are to be found among them." In this connection the observations of ROUS, McMASTER and BROWN (*Proc. Soc. Exper. Biol. and Med.*, 1922, 20, 128), made under controlled conditions in dogs, are of interest. By a special method it was possible to join a rubber tube to the common duct of a dog and collect the bile under sterile conditions for months. In a series of 12 dogs calculi were found in the collecting systems in 6, in 3 of which the bile had remained sterile. In 2 of these 3 instances the calculi gradually filled the 2 mm. lumen of a glass cannula on the wall of which they were sessile, and gave rise to obstruction. Once

this happened within twenty-one days of intubation. No calculi occurred in the absence of organic débris. The calculi were found only on the walls of rubber and glass and never in the ducts. They consisted of calcium bilirubinate and calcium carbonate, with a scaffolding of organic material. These observations indicate that the infection is not the essential factor in cholelithiasis, although the authors state "that it frequently plays the determining role is equally certain." This it would seem to do by damaging the duct wall with resultant desquamation and by lessening the ability of the bile ducts to excel the organic débris which induces the deposition of solids, catching and retaining potential nuclei for stone formation.

A Functional and Anatomical Study of the Excretion of Hemoglobin by the Kidney.—By histological methods and by determining the amount of hemoglobin in the urine, FUKUDA and OLIVER (*Jour. Exper. Med.*, 1923, 37, 83) found that after injecting hemoglobin into the circulatory system of rabbits their results were best explained by the assumption of a filtration of hemoglobin through the renal glomerulus and an additional excretion of it by the tubule cells. The amount of hemoglobin in the urine was determined by Newcomer's method, with a colored glass standard and the Duboscq colorimeter. Hemoglobin was introduced intravenously in the dosage of 0.06 mg. per kilo, and specimens of urine were recovered by catheter every fifteen minutes for eight periods and after thirty and seventy-five minutes. There was a steady rise in the amount of hemoglobin excretion, reaching the maximum in 7 out of 10 experiments in the second and third periods and the falling gradually with occasional levels of constant excretion or even slight rises. In all of the experiments but two the "major curve" of hemoglobin excretion bore no constant relationship to the amount of water excreted. The microchemical demonstration of the iron of hemoglobin was accomplished by boiling in water or Müller's solution for two minutes, dehydrating in alcohol, embedding in paraffine, freeing of paraffine, placing in peroxide (3 per cent) for eighteen hours and applying equal parts of potassium ferrocyanide (2 per cent) and hydrochloric acid (1 per cent) for one hour and counter-staining with carmine. Rabbits killed at intervals of from fifteen minutes to two hours after intravenous injection of normal saline, and then hemoglobin solution, showed the same picture. The convoluted tubules and the ascending limbs of Henle's loops were heavily stained as well as the masses of hemoglobin in the ducts of Bellini. In Bowman's capsule the hemoglobin was more dilute in quantity. The authors believe that the absorption aids in the concentrating process of the hemoglobin and is most marked in the collecting tubules. They call attention to a similar mechanism of glomerular filtration and tubule excretion in operation in the excretion of urea, as shown by OLIVER (*Jour. Exper. Med.*, 1921, 33, 177).

The Relation between Chronic Irritation of Peritoneal Mesothelium and the Formation of Adhesions.—Having demonstrated previously that the peritoneal mesothelium of rats which received repeated injections of solutions of glucose underwent certain changes of a morphological character which were not followed by adhesions, CUNNINGHAM

(*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 342) employed various types of mild irritants to determine to what extent such changes could be produced without sufficient injury occurring to cause the development of adhesions. The best results were obtained with laked heterogenous blood. Cats were injected intraperitoneally with 10 to 20 cc of laked rabbits' blood, made isotonic with NaCl, twice weekly over a period of three to six months. It was found that the peritoneum, under the conditions of the experiment, was often made up of two or three layers of cuboidal or columnar cells, attaining at times a thickness of 20 micra. Not a single adhesion occurred, the peritoneal lining being entirely adequate to prevent the formation of adhesions. The author concludes "that the presence of a complete layer of peritoneal lining cells, no matter how much their morphological appearance may be altered by such irritations as those used, is entirely sufficient to prevent the adhesion of the two layers of peritoneum and thus prevent adhesions."

A Cytological Study of the Nature of Rickettsia in Rocky Mountain Spotted Fever.—"Conflicting views have been expressed regarding the nature of Rickettsia in Rocky Mountain spotted fever and other diseases. While some believe they are true microorganisms, others remain entirely unconvinced." In the belief that the exact relation of the organisms to normal and abnormal constituents might be susceptible to analysis by methods elaborated in the field of general cytology, NICHOLSON (*Jour. Exper. Med.*, 1923, 37, 221) examined tissues from guinea-pigs one, two, three, four and five days after the first day of characteristic fever encountered in the experimental production of the disease. Giemsa's stain was employed for the coloration of Rickettsia, the preliminary fixation being accomplished by Regaud's fluid (4 parts of 5 per cent solution of potassium bichromate and 1 part of commercial formalin). For a comparison of Rickettsia with normal and abnormal constituents the aniline-fuchsin and methyl-green method of Bensley was employed for mitochondria, the iron-hemotoxylon technic for phagocytosed hemoglobin and Kyes' method for Gram-positive organisms in tissues. It was found that the Rickettsia of Rocky Mountain spotted fever were easily differentiated from the mitochondria, phagocytosed blood pigment, nuclear debris and all other known cellular constituents. Although they were lodged within the cytoplasm of endothelial cells they were not observed to establish any definite relations with the nucleus or with other cellular components. Diplobacillary forms were most abundant in the early stages of the reaction and single bacillary bodies toward its termination. Wolbach's study of the distribution of specific lesions with accompanying organisms in the tissues of guinea-pigs was confirmed and extended by the author.

Further Notes on Experimental Measles in Rabbits and Monkeys.—NEVIN and BITTMAN (*Jour. Infect. Dis.*, 1923, 32, 33) were able to confirm their previously reported experimental observations, having to do with the production of measles in rabbits and monkeys by additional inoculations. Blood from 3 human cases of measles in the second day of their illness was injected into two series of animals. In the first series the virus, as occurring in the pooled blood of 2 human

of slow germination as observed in heated cultures. Heat injury, if it plays any part at all, must be a secondary factor prolonging the period of dormancy of the individual spore beyond its normal limit. Relative permeability of the spore wall is suggested as a possible common factor affecting both dormancy and heat resistance and accounting for the apparent relation which has been observed between length of time of exposure of the spores to heat and subsequent length of germination time. Fractional sterilization as generally practised does not insure absolute sterilization of material containing spores of *B. botulinus* because of the slow germination of many of the spores. The problem of dormancy has a bearing on much of the experimental work dealing with spore-bearing bacteria, particularly that in which conclusions have been based on negative cultures.

Studies on the Manner in which the Toxin of *Clostridium Botulinum* Acts upon the Body. The Effect upon the Voluntary Nervous System.—DICKSON and SHEVKY (*Jour. Exp. Med.*, 1923, 37, 711) have found that botulinus toxin acts upon the fibers of the parasympathetic nervous system. DICKSON and SHEVKY (*Jour. Exp. Med.*, 1923, 38, 327) found that the toxin of Types A and B exerts an influence upon the endings of the motor fibers of the voluntary nervous system which leads to a marked susceptibility to fatigue. It has not been determined whether the damage is in the anatomical nerve endings of the somatic motor nerve fibers or upon the myoneural junction, but it is not of the nature of an organic destruction of tissue. There is no effect upon the sensory fibers of the peripheral nerves. The muscle cells of the smooth and striated muscles are not affected. The disturbances in function which have been demonstrated in the voluntary and involuntary nervous systems fully explain the characteristic signs and symptoms of botulinus intoxication.

Plague-infected Rats without Visible Lesions.—WILLIAMS and KEMMERER (*Pub. Health Rep.*, 1923, 38, 1873) record observations on plague in rats in Gulf Coast cities of the United States. In New Orleans rats were found which had poorly defined lesions of the disease and were detected only by the inoculation of test animals, though some showed organisms in smear preparations that were consistent with the plague germ. In Galveston a number of rats which showed no gross evidence of disease were found to harbor organisms virulent for guinea-pigs. It is suggested that the inoculation of material from several rats into one test animal affords a convenient means of detecting infection that would otherwise pass unnoticed.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

FEBRUARY, 1924

ORIGINAL ARTICLES.

THE CLINICAL SIGNIFICANCE OF THE PATHOLOGICAL
CHANGES IN HODGKIN'S DISEASE.

BY DOUGLAS SYMMERS, M.D.,

DIRECTOR OF LABORATORIES, BELLEVUE AND ALLIED HOSPITALS, NEW YORK.

(From the Pathological Laboratories of Bellevue Hospital.)

IN 1832 Hodgkin called attention to a disease characterized by progressive enlargement of the lymph nodes associated with enlargement of the spleen.¹ Five of the 7 cases originally described by him were undoubtedly types of lymph-node tuberculosis or syphilis, or of leukemia, lymphosarcoma or pseudoleukemia, but the remaining 2 were almost certainly genuine examples of the affection to which Wilks,² in 1856, gave the name of Hodgkin's disease. Over a space of nearly seventy years after the appearance of Hodgkin's paper innumerable contributions were made to the subject, and Hodgkin's disease came to represent an apparently hopeless conglomeration of lymph-node and splenic enlargements. In 1899, however, Sternberg³ established the fact that Hodgkin's disease is a histological entity, the changes in the lymph nodes and elsewhere consisting in the appearance of a connective-tissue reticulum supporting variable numbers of lymphocytes, together with mononuclear and multinuclear giant cells, with or without an admixture of eosinophiles. This histological composite is now generally accepted as the criterion on which the diagnosis of Hodgkin's disease is to be made.

During the past fifteen years 14 cases of Hodgkin's disease have been encountered in the pathological laboratories of Bellevue

Hospital among 8485 autopsies. These cases have been made the subject of clinical, anatomical and histological studies, and form the basis of the present communication. From the pathological viewpoint they are divisible into two groups and are so arranged in this paper. In the first group are included those cases in which the characteristic histological changes are limited to the lymphoid tissues, that is to say, to the lymph nodes proper and to the lymphoid follicles in the spleen and in the walls of the portal vessels and to other residual foci in the lungs, bone-marrow, kidney, adrenal, subcutaneous tissues, serous membranes, etc. In the second group are included those cases in which, in addition to changes of the same sort and in the same localities, the disease mechanically infiltrates skeletal muscles, bloodvessels, serous membranes and loose tissues, and, by direct pressure, erodes bone or partially replaces viscera.

In preparing these cases for publication irrelevant detail has been omitted, and only those facts are offered for consideration which appeared to be of value in the present connection. This presentation comprises, among other things: (1) A series of cases in which the pathological changes were confined to the lymphoid system, including (a) a newly recognized variety of Hodgkin's disease of the liver, (b) a discussion of Hodgkin's disease of the spleen as a clinical and pathological entity, and (c) an example of Hodgkin's disease associated with changes in the skin resembling the so-called acanthosis nigricans; (2) a series of cases showing invasive destruction of the skeletal muscles; (3) a discussion of Hodgkin's disease of the thymic remains attended by invasion and destruction of neighboring tissues; (4) an analysis of the lymph-node changes, with particular reference to the rarity of massive Hodgkin's disease of the cervical nodes and the frequency of predominant abdominal, or of predominant combined abdominal and thoracic involvement; (5) a discussion of the changes in the several viscera; (6) a theory of the histogenesis of Hodgkin's disease as an affection of the hemolytopoietic system; (7) a consideration of the apparent kinship of the disease to chronic myelogenous leukemia; (8) a discussion of the nature of Hodgkin's disease—whether inflammatory or neoplastic; (9) a résumé of its symptoms and signs, duration, treatment, etc.

CASE I. Group I. Changes Confined to Lymphoid Tissues.—H. M., a school-girl, aged sixteen years, was admitted to Bellevue Hospital, October 28, 1919; died January 7, 1920. She stated that three years previously she had noticed a swelling on the left side of the neck that was about the size of a cherry. The growth was painless and continued to enlarge to such an extent that within five months it had attained the size of a small orange. Two years later the patient noticed a small swelling on the right side of the

neck, apparently of the same nature as that on the left. In the winter of 1918 she was afflicted by the prevailing pandemic pneumonia. During that time the nodes in the neck disappeared almost completely. Shortly thereafter, however, they again enlarged and increased rapidly in size, those on the right side attaining greater proportions than those on the left. In the course of the next six months the cervical nodes received ten roentgen-ray exposures at the hands of an extramural physician. The patient was now very weak, short of breath and suffered from a productive cough.

Physical examination showed, among other things, enormous enlargement of the supraclavicular lymph nodes, together with those of the submaxillary region, the anterior and posterior cervical nodes and the nodes of the right axilla. The neck measurements at the upper level showed a circumference of 42.5 cm., 46 cm. at the center and 52 cm. at the base. Early in January the patient's cough became so distressing as to interfere with sleep, and she complained of difficulty in swallowing. Three days later the skin and conjunctivæ assumed a faint icteroid tint, which gradually deepened until the time of death. The inguinal nodes were not enlarged. The red cells numbered 2,300,000; hemoglobin, 35 per cent; white cells, 7000; polymorphonuclear neutrophils, 76 per cent; lymphocytes, 20 per cent; large mononuclear cells, 2 per cent; transitionals, 2 per cent. A superficial lymph node was excised and the pathological diagnosis was made of Hodgkin's disease.

Duration of symptoms: Three years and two months.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the cervical lymph nodes and of the lymph nodes at the superior aperture of the thorax; extensive hyperplasia of the periaortic and peripancreatic nodes and those at the hilus of the liver; solitary nodule in the neck of the gall-bladder and in the mucosa of the left bronchus; slight enlargement of peribronchial lymph nodes; splenomegaly with innumerable nodular foci; multiple nodules in liver.

Histology. Microscopical examination of enlarged lymph nodes from the neck showed a fine connective-tissue reticulum, imbedded in which were comparatively small numbers of lymphocytes, numerous eosinophiles, moderate numbers of large mononuclear cells and a profusion of multinuclear giant cells of the myeloid type. In addition there were numerous wide, streak-like or intercommunicating necrotic foci, many of which were infiltrated by small, poorly chromatic cells of the fibroblastic type resting in a stroma of indefinite composition. The smaller bloodvessels in or near the necrotic areas were partially or completely obliterated as a result of heaping up of the lining endothelium and thickening of the walls. The microscopical changes in the spleen were essen-

tially identical with those in the lymph nodes. The liver showed numerous large and small collections of cells lying in the periportal spaces that were composed of a reticulum supporting prominent numbers of eosinophiles and eosinophilic myelocytes, lymphocytes and mononuclear and multinuclear giant cells. Smears from the marrow of the sternum showed numbers of well-preserved red corpuscles, numerous normoblasts, many neutrophilic myelocytes, a few eosinophilic myelocytes, eosinophiles, large mononuclear cells and myeloblasts. Sections from the marrow were richly cellular, showing large numbers of multinuclear giant cells. In places the marrow was permeated by fibroblasts.

Comment. This case affords an example of the readiness with which the structures of the neck and thorax, notably the trachea and bronchi and the esophagus, are able to adapt themselves to gradually increasing pressure for a long period of time before giving rise to symptoms, as shown by the fact that the patient did not complain of pressure disturbances until after the lapse of at least two years of widespread lymph-node involvement in the neck and thorax. Moreover, in spite of compression of the structures of the portal space by masses of enlarged lymph nodes, the biliary drainage system was able to function for a long period in such efficient fashion that obstructive changes occurred only as a terminal event. The case is also noteworthy as illustrating the almost complete disappearance of the enlarged lymph nodes in the neck after a siege of infection, followed by progression when the infection had subsided.

The histological changes in the cervical lymph nodes and elsewhere permit of several deductions of practical value, particularly in view of the fact that the cervical nodes had been subjected to roentgen-ray therapy and were the seat of necrotic foci, attended by obliteration of the smaller bloodvessels, followed by an attempt to substitute the dead areas by connective tissue. These changes are comparable to those which, it is claimed, occur in certain malignant growths after roentgen-ray therapy. In the case under consideration, however, histological alterations identical with those in the lymph nodes of the neck, which had been subjected to radiation, were also found in the spleen and in the enlarged lymph node in the wall of the gall-bladder, neither of which had been exposed to the roentgen-ray. Moreover, identical necrotic and replacement changes were observed in the lymph nodes and spleen in other cases of this series where the roentgen-ray had not been employed at all.

This is the only case of massive Hodgkin's disease of the cervical lymph nodes to be encountered in this series.

CASE II.—The patient, J. W., aged sixty-six years, was admitted to Bellevue Hospital on October 7, 1916, complaining of pain in

the left side of the abdomen, swelling of the feet and cough. He stated that in October of the previous year he had entered another hospital because of enlarged lymph nodes on the right side of the neck; the opposite side was not affected. While in the hospital one of the enlarged lymph nodes was removed and a diagnosis of Hodgkin's disease was made. Soon after leaving the hospital the swelling of the neck increased, and he began to have sharp pains in the abdomen to the left of the umbilicus. This pain, in time, became continuous and interfered with sleep. Just before entering Bellevue Hospital the patient noticed that his feet were swollen.

At the time of admission to Bellevue Hospital physical examination showed that there were lymph nodes on the right side of the neck that combined to form a large mass. A few enlarged lymph nodes were likewise present on the left side of the neck and in the right axilla and in both inguinal regions. The abdomen was distended by fluid. The spleen was palpated 8 cm. below the costal margin in the left anterior axillary line and was tender. The liver was not felt. Five days after entering Bellevue Hospital the patient died of croupous pneumonia. At the time of admission the white cells numbered 18,000, of which there were 94.5 per cent polymorphonuclear neutrophiles, 2.5 per cent lymphocytes, 1.5 per cent large mononuclear cells and 1.5 per cent transitionals.

Duration of symptoms: One year and three months.

Autopsy Findings. Hodgkin's disease affecting the nodes of the right side of the neck, right axillary and both inguinal regions and peripancreatic, periaortic and iliac groups; extensive replacement of vertebræ; multiple nodules in liver and spleen; minute nodules in both kidneys; ascites.

Histology. The most striking feature in the histology of the lymph nodes removed from various parts of the body and of the spleen was to be found in the pronounced overgrowth of connective tissue, which in places was mature, in other places rather richly fibroblastic. In the connective tissues, arranged diffusely or as islands or streak-like areas, were lymphoid cells, relatively large numbers of large mononuclear cells and a liberal sprinkling of multinuclear giant cells; eosinophiles were scarce. In the periportal tissues were large collections of cells of identical composition. Preparations from the vertebræ showed different histological changes in the same section. In places the marrow spaces were filled by tissue of the same sort as that encountered in the lymph nodes and elsewhere. In other places the marrow spaces were occupied by granulation tissue, in which were eosinophiles and eosinophilic myelocytes, large mononuclear cells and polymorphonuclear neutrophiles. In such areas myeloid giant cells were conspicuous by their absence. In still other parts the bone-marrow was rich in cells of the lymphocytic and plasma type, together with large mononuclear and multinuclear giant cells, eosinophiles

and eosinophilic myelocytes, representing, apparently, hyperplasia of cells normally encountered in the marrow.

Comment. This case represents one of combined cervical and abdominal Hodgkin's disease without participation of the thoracic nodes, together with foci in the liver and kidney, a markedly enlarged and sclerotic spleen and extensive invasion of the vertebral column.

CASE III.—T. F., a Greek laborer, aged twenty years, was admitted to Bellevue Hospital, January 25, 1917, and died March 3, the same year. The patient complained chiefly of dyspnea of a month's duration. He stated that six months previous to admission he had noticed swelling of the ankles, followed a short time thereafter by enlargement of the inguinal lymph nodes on both sides.

Physical Examination. The inguinal lymph nodes on both sides and the nodes of the femoral chain on the right side were enlarged. Within a month after admission the patient became generally edematous and the abdomen was distended by fluid. A month before death a few slightly enlarged lymph nodes appeared in the cervical region. The blood count revealed 3,800,000 red cells; 2200 white cells, of which 85 per cent were polymorphonuclear neutrophils, 10 per cent lymphocytes, 2 per cent large mononuclears and 3 per cent transitionals. Microscopical examination of sections made from an excised inguinal lymph node showed the histology of Hodgkin's disease with numbers of mononuclear and multinuclear giant cells.

Duration of symptoms: Approximately seven months.

Autopsy Findings. Hodgkin's disease of abdominal and inguinal lymph nodes with slight involvement of the cervical nodes; nodules in the spleen and liver, in the parietal and frontal bones and in the posterior urethra; edema of lower extremities due to compression of iliac veins by enlarged lymph nodes; bilateral hydrothorax; ascites; emaciation; exfoliative dermatitis; suppurating surgical incisions in both groins; secondary suppurative lymphadenitis of abdominal lymph nodes.

Histology. Enlarged lymph nodes from different localities and sections from the spleen, ileum and appendix showed the characteristic changes of Hodgkin's disease—a reticulated stroma supporting lymphocytes, large mononuclear and multinuclear giant cells and a few eosinophiles. Sections from the bone-marrow showed lymphocytic and plasma cells in abundance, eosinophiles and eosinophilic myelocytes and typical mononuclear giant cells, together with an occasional multinuclear giant cell, the morphology of which was indistinguishable from those normally encountered in the marrow. The vast majority of the giant cells, however, were atypical, that is to say, their nuclei were extremely dense

and deeply staining and assumed all sorts of odd shapes—irregularly rounded or oval or semilunar, rectangular or dumbbell-shaped, jagged or stellate—the cytoplasm staining faintly pinkish. On account of the presence of large numbers of polymorphonuclear neutrophiles in the other tissues, particularly in the enlarged lymph nodes, it was impossible to identify atypical giant cells in sections. In the liver, however, microscopical examination of the nodular foci showed a connective-tissue stroma supporting large numbers of mononuclear cells and a fairly rich sprinkling of multinuclear giant cells and, among the latter, atypical forms, corresponding to those met with in the bone-marrow, were to be seen, the nodules in the liver presenting only a few polymorphonuclear neutrophiles to obscure the histological picture of Hodgkin's disease.

Comment. In this case correlation of the clinical and anatomical findings points to the conclusion that the first clinically detectable signs of disease were dependent on enlargement of the abdominal lymph nodes, as shown by edema of the lower extremities followed by enlargement of the inguinal nodes. The cervical nodes were involved late and then only to a negligible extent, while the thoracic nodes escaped. Another feature of interest is to be found in the occurrence of atypical multinuclear giant cells in the bone-marrow and the identification of similar cells in the nodules in the liver, as indicating that the cells in the liver were derived from the bone-marrow by the process of embolism.

Finally, it is to be observed that the patient died as a result of secondary infection following the removal of enlarged inguinal lymph nodes for purposes of diagnosis. In this connection it is to be recalled that surgical wounds of the groin are apt to become infected easily, sometimes even though the utmost care be exercised, as, for example, in hernia operations, and that such infections are difficult to control. In Hodgkin's disease removal of the inguinal lymph nodes for diagnosis is, in my opinion, a procedure to be undertaken only in extraordinary circumstances, and then at the hands of a surgeon who is prepared to exercise every precaution against infection. It is not an operation to be entrusted to the casual.

CASE IV.—J. S., male, aged forty-seven years, was admitted to Bellevue Hospital, March 23, 1917, and died April 4, the same year.

Physical examination revealed slight cyanosis, particularly of the extremities. There were signs of fluid at the bases of both lungs. The superficial veins of the abdominal wall were dilated, the abdomen was distended and there was shifting dullness in both flanks. Paracentesis released 2000 cc of yellow cloudy fluid from the left chest. On March 3, 1500 cc of fluid were removed from the abdomen, after which the liver and spleen were easily palpated.

There was a large mass of lymph nodes in the left groin and a similar, but smaller, collection on the right side. Enlarged lymph nodes were palpated in both axillæ, but the cervical region was free. The white cells numbered 13,200; polymorphonuclear neutrophiles, 92 per cent; small lymphocytes, 5 per cent; large mononuclears, 2 per cent; transitionals, 1 per cent.

Duration of symptoms: Doubtful.

Autopsy Findings. Hodgkin's disease of the abdominal and thoracic lymph nodes with relatively slight involvement of the axillary and inguinal groups; splenomegaly; nodules in liver and in cortices of kidneys; involvement of bone-marrow; ascites; hydrothorax.

Histology. The lymph nodes and spleen, the perilobular spaces of the liver and the bone-marrow showed a fibroblastic connective-tissue reticulum, scattered through which were relatively small numbers of lymphoid cells and numerous eosinophiles and eosinophilic myelocytes, arranged diffusely or in groups, and variable numbers of large mononuclear cells and myeloid giant cells.

Comment. This case is one of predominant involvement of the abdominal nodes, with associated enlargement of the peribronchial lymph nodes, without, however, any indication of participation of the nodes in the neck.

CASE V.—The patient, M. B., female, aged twelve years, was admitted to Bellevue Hospital on December 29, 1921, and died February 6, 1922. Her mother stated that six years previously she had noticed a small mass on the right side of the child's neck and that the patient vomited frequently. She took the child to the Kings County Hospital in Brooklyn, where an enlarged node was excised and, according to the mother, was reported as Hodgkin's disease. Subsequently the patient suffered a number of attacks characterized by weakness, anorexia, vomiting and pain in the upper part of the abdomen. During several of these attacks she was jaundiced. Six weeks before admission to Bellevue Hospital, the patient suffered an attack attended by jaundice and by pains in the abdomen of such severity that she fainted on several occasions.

Physical Examination. An emaciated and jaundiced girl, in whom the liver and spleen were palpable. The skin presented signs of bran-like desquamation. At the angle of the jaw on the right side was a nodular mass, about 2 cm. in length. A few similar nodules were present in the front of the neck on the right side. The roentgen-ray report was to the effect that there were enlarged lymph nodes at the root of both lungs. The blood count revealed 2,568,000 red cells, 60 per cent hemoglobin and 6700 white cells, of which 69 per cent were polymorphonuclear neutrophiles, 24 per cent lymphocytes and 7 per cent eosinophiles.

Duration of symptoms: Six years and one month.

Autopsy Findings. Hodgkin's disease with massive enlargement of the abdominal lymph nodes and extensive changes in the nodes of the thorax; slight enlargement of nodes of neck; splenomegaly; obstructive jaundice; chronic passive congestion of liver with multiple nodular foci; generalized exfoliative dermatitis.

Histology. Microscopical examination of lymph nodes removed from different parts of the body showed the presence of irregular but widespread overgrowth of rather poorly cellular fibrous tissue. In some of the nodes the architecture was altered to such an extent that the histological diagnosis of Hodgkin's disease could be made, if at all, only with difficulty. Other lymph nodes were extensively but irregularly replaced by sclerotic connective tissue supporting relatively scanty numbers of lymphocytes, among which large mononuclear cells were scattered in fair abundance, together with an occasional giant cell of the myeloid type. Eosinophiles could not be seen. The spleen likewise showed extensive replacement by connective tissue, particularly in the region of the Malpighian follicles, the vessels of which were practically always occluded or their lumina reduced to a minimum, the lymphoid remains, if any, lying in thick bundles or streaks of plaque-like, hyalinized connective tissue. In the spleen giant cells could not be detected. For the greater part, the perilobular tissues in the liver were occupied by rounded, oval or streak-like collections of lymphocytes with a few mononuclear giant cells and, rarely, a giant cell of the myeloid type.

Comment. This case is one of a young girl who, for a period of slightly more than six years suffered from attacks characterized by nausea, vomiting and pain in the upper abdomen, attended by several attacks of jaundice. Anatomically, the disease was marked by enormous enlargement of the abdominal lymph nodes. Nodes which compressed the structures at the hilus of the liver accounted for the jaundice. The peribronchial lymph nodes were enlarged, although to a less extent than those in the abdomen, and the nodes of the neck were only slightly involved. The patient complained of no symptoms referable to the chest with the exception of a cough of short duration. The most striking feature in the histological examination consisted in the widespread overgrowth of connective tissue in certain of the lymph nodes and in the spleen. In the latter locality, it was particularly noticeable, occurring to such an extent as to obscure the characteristic histology of Hodgkin's disease.

CASE VI.—The patient, a man, aged thirty-nine years, was admitted to Bellevue Hospital for the second time on August 10, 1916, and died April 18, 1917. He stated that three years previously he had observed small nodules in the neck and axilla and that in the course of the next year, these increased to such an extent that he submitted to a surgical operation for their removal.

He first came to Bellevue Hospital, in 1915, because of recurrence of the growths, and a small nodule was removed for diagnosis. At the time of the patient's re-admission to Bellevue Hospital, in 1916, he complained of pains in the back and of intervals of diarrhea alternating with constipation. The spleen was palpable $7\frac{1}{2}$ cm. below the left costal margin and the liver 5 cm. below the costal margin on the right side. In the right upper quadrant of the abdomen was a large, firm mass, lying to the right of the umbilical region, and there were slightly enlarged nodes in the neck and axillary and inguinal regions. There were no signs of fluid to be detected in the abdomen, but the scrotum was markedly edematous. In the interval between March 31 and April 10, 1917, the patient's spleen and the enlarged nodes in the neck were subjected to roentgen-ray exposures, after which the spleen is said to have diminished in size by about 5 cm., as measured by palpation.

Duration of symptoms: Three years and eight months.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the abdominal lymph nodes; moderate hyperplasia of the mediastinal and peribronchial nodes; splenomegaly; multiple nodular foci in liver.

Histology. Microscopical examination of the lymph node removed from the neck in 1915 showed a thickened and hyalinized capsule from which trabeculae penetrated downward for variable distances. In the intervals between the trabeculae were collections of lymphoid cells, a few large mononuclear cells and an occasional giant cell of the myeloid type. Eosinophiles were not noted. In certain of the lymph nodes removed at autopsy the degree of connective-tissue replacement was even more pronounced than in the node excised during life; the lymphoid cells were visible only as minute islands widely separated by masses of hyalinized fibrous tissue, the architecture of the nodes being so altered that the diagnosis of Hodgkin's disease could not be made on the basis of histological appearances. In other words, the microscopical changes in lymph nodes removed, respectively, three years before radiation and two weeks after radiation, showed changes which were qualitatively identical. Microscopical examination of the spleen, which had several times been exposed to radiation during a period of two weeks immediately before death, showed widespread replacement of the normal architecture by streak-like bands of cellular, well-fibrillated connective tissue, between which were large collections of lymphoid cells and numbers of mononuclear and multinuclear giant cells. The smaller bloodvessels in the spleen, almost without exception, showed heaping-up of the lining endothelium, thickening of the walls and diminution or occlusion of the lumina. It was obvious that the fibrotic and vascular changes were of such maturity as to eliminate any possible relationship to the roentgen-ray exposures that had been made in the last few weeks of life.

In the perilobular spaces of the liver were large and small collections of cells consisting of a delicate reticulum, likewise enclosing lymphocytes and mononuclear and multinuclear giant cells. Among the latter were many with atypical nuclei.

CASE VII.—F. R., male, aged forty-eight years, was admitted to Bellevue Hospital, September 22, 1915, and died December 12, 1915. His complaint consisted of periodical stabbing pains in the lumbar region, radiating toward the spleen and testicle, and of areas of hyperesthesia and exquisite tenderness over the sternum, together with frequency of urination, attended by a sensation of scalding. He stated that he had lost 40 pounds in weight in the previous three months.

On admission a few enlarged lymph nodes were present on the left side of the neck and in the corresponding axilla, and smaller ones in the neck on the right side. The spleen was palpable $2\frac{1}{2}$ cm. below the costal margin and as far forward as the nipple line. The inguinal nodes on both sides were greatly enlarged. In the abdomen a firm, fixed mass was felt in the left lower quadrant that was about 12 cm. in length, extending from the median line into the left flank. The same mass was palpable through the rectum. A month after admission the lymph nodes on the left side of the neck had diminished appreciably in size, while the spleen had increased so that it was palpable almost as far forward as the middle line. Cystoscopic examination showed a smooth mass which elevated the posterior bladder wall between the orifices of the ureters as far downward as the internal sphincter. Red cells numbered 2,910,000; white cells, 5200, of which 64 per cent were polymorphonuclear neutrophils, 21 per cent small lymphocytes, 6 per cent large mononuclear cells and 9 per cent transitionals. Wassermann reaction negative. An excised lymph node revealed the histology of Hodgkin's disease.

Duration of symptoms: Seven months.

Autopsy Findings. Hodgkin's disease, with enormous enlargement of the abdominal and pelvic nodes, attended by elevation of the posterior wall of the urinary bladder; massive splenomegaly; massive solitary nodule at transverse fissure of liver surrounding portal vein; multiple small nodules in kidneys.

Histology.—Microscopical examination of the enlarged lymph nodes and of the foci in the spleen, kidney and liver showed a fine connective-tissue reticulum which enclosed a few lymphocytes and prodigious numbers of large mononuclear cells, together with a faint sprinkling of multinuclear cells of the myeloid type.

Comment. In this case the nodes in the abdomen presented an extraordinary degree of enlargement, while the thoracic nodes escaped entirely and those of the neck were enlarged to a very slight extent. Perhaps the most interesting individual feature in

the case consists in the fact that at the transverse fissure of the liver was a solitary massive nodule which surrounded the portal vein and appeared to spring from its walls. Microscopical examination of this nodule indicated that the mass in question had actually arisen as a result of hyperplasia of residual lymphoid collections in the walls of the portal vein—a fact which, taken in connection with the anatomical and histological findings in the next case to be described, emphasizes the importance of the vascular structures in the liver in Hodgkin's disease from the standpoint of histogenesis.

CASE VIII. Predominant Enlargement of the Liver in Hodgkin's Disease.—S. P., female, aged forty years, was admitted to Bellevue Hospital, April 12, 1921, and died twelve days later. She complained of cough of two weeks' duration, but principally of enlargement of the abdomen that had been progressing for a period of three months, attended by pains in the epigastrium and chest. At the time of admission the patient was profoundly emaciated. The skin was tinged slightly yellow. The abdomen was prominent and there were signs of a fluid wave and of shifting dulness. The lower edge of the liver was palpated at the level of the umbilicus. The spleen was not felt. After paracentesis and the removal of 4400 cc of clear yellow fluid the edge of the spleen was palpated in the anterior axillary line. Red cells numbered 2,400,000; hemoglobin, 18 per cent; white cells, 14,800, of which 59 per cent were polymorphonuclear neutrophils, 39 per cent lymphocytes and 2 per cent transitionals.

Duration of symptoms: Three months (?).

Autopsy Findings. The abdomen contained about 500 cc of clear fluid. The liver was enormously enlarged, the lower margin resting at the level of the umbilicus. Its shape was normal. The surface was smooth, except for a number of minute whitish nodules, the largest of which were about 5 mm. in diameter. On section, the substance of the liver was permeated by large, smooth, opaque bands of fibrous tissue which followed the distribution of the portal system. At the time of necropsy it was estimated that two-thirds of the parenchyma was thus replaced (Fig. 1). On cross-section the fibrous bands were rounded in shape, often approximating the size of one's little finger, and were distinctly differentiated from the remnants of liver tissue and frequently presented at the center a minute dimple, corresponding to the cut-end of a bloodvessel. In other places were similarly rounded masses which were only a few millimeters in diameter. Between these and the larger ones were fibrous areas of different gradations in size. The liver tissue in the immediate vicinity presented evidences of compression, the lobular remnants being small and irregular in shape. In places were large reddish splotches, suggesting hemorrhagic extravasations.

The mesenteric and retroperitoneal lymph nodes were moderately increased in number and varied in size from 1 to 3 cm. On section they were firm and presented a smooth, whitish, translucent surface. No other enlarged lymph nodes were encountered. The spleen was normal in size.

Histology.—Microscopical examination of the liver showed extensive replacement of the parenchyma by connective-tissue bands which consisted of a pinkish staining, homogeneous or poorly fibrillated matrix in which were fairly large numbers of small, lightly staining nuclei of different shapes, some short and plump,

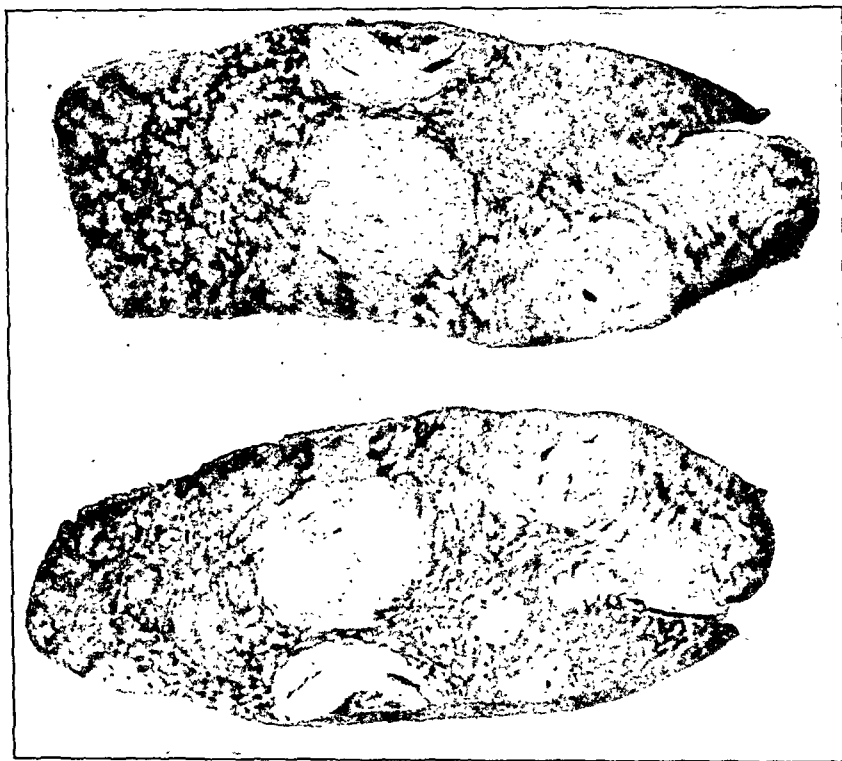


FIG. 1.—Case VIII. Photograph of tissue from the liver showing extensive sclerotic changes. The larger whitish masses represent thickened portal veins which have fused. In them the lumina are sometimes still visible as minute dots appearing black in the illustration. The smaller whitish masses likewise represent thickened veins. At necropsy, it was estimated that two-thirds of the liver substance had been replaced in this fashion. A few enlarged lymph nodes were present in the abdominal cavity and histologically showed the characteristic changes of Hodgkin's disease. The extensive sclerotic changes in the walls of the portal veins are believed to represent a new phase in the pathology of Hodgkin's disease.

others drawn out at one end, others oat-shaped, few of them clean-cut spindles. The connective-tissue bands occupied the portal spaces and expanded in such fashion as to produce pressure atrophy of the liver lobules and the bile ducts, remnants of which could be seen lying in them as streaks or islands of different shapes. In practically every one of them was a small portal vessel encircled by a mantle of lymphocytic cells, among which, in many instances,

were large mononuclear cells and, occasionally, a multinuclear giant cell (Fig. 2). In other instances the lumen of the small portal vessels was occluded or obliterated, and arranged around the remains were collections of lymphocytes, a relative preponderance of large mononuclear cells and an occasional giant-cell—the whole set in the midst of a rounded mass of fibrous tissue. In still other places, particularly in the periportal spaces between the compressed liver lobules at the periphery of the large fibrous bands, the connective tissue was arranged in small streaks or patches, and was delicately fibrillar and infiltrated by lymphoid cells, representing, apparently a localized reactive process. None of them showed the

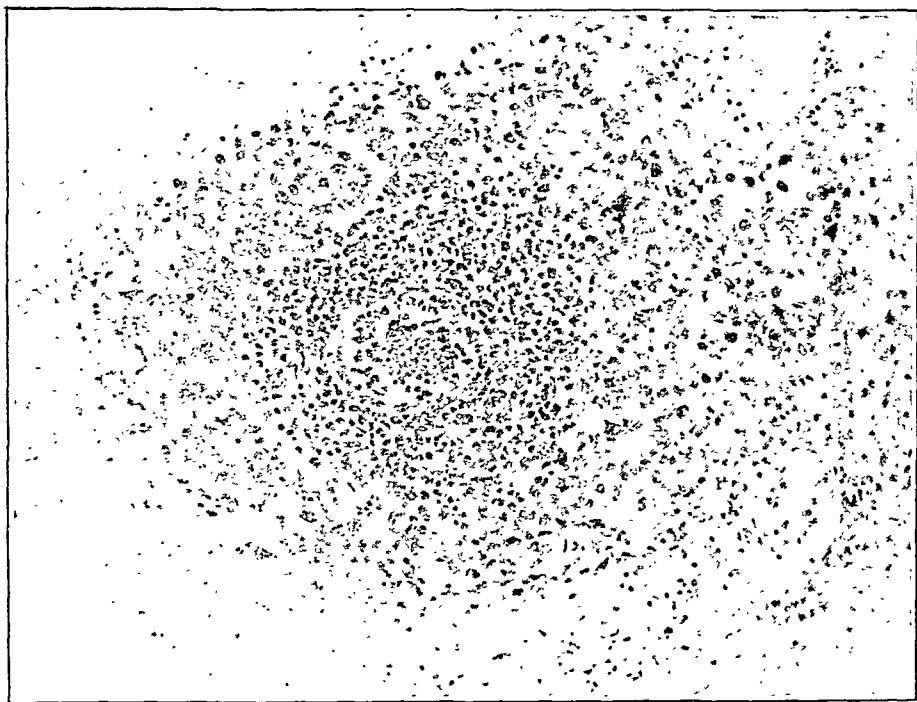


FIG. 2.—Case VIII. Photomicrograph of small portal vein surrounded by a collection of small lymphocytes, large mononuclear cells and an occasional atypical multinuclear giant cell.

histological changes of Hodgkin's disease, the latter being confined to the walls of the portal vessels or their remains. Finally, numerous hemorrhagic extravasations were visible, practically always among the compressed lobular remnants, due, apparently, to vascular injury induced by the pressure of the connective-tissue masses growing around the portal vessels. In the substance of the spleen microscopic examination showed great thickening of the larger veins, the walls of which were reinforced by poorly nucleated connective tissue in which were groups of lymphoid cells and a few cells of the large mononuclear type, together with conspicuous numbers of atypical multinuclear giant cells (Fig. 3). Microscopically the splenic pulp was unchanged. The lymph nodes

were extensively but irregularly replaced by fibrous tissue, which was poorly nucleated and presented a glazed, hyaline appearance. In the intervals were collections of lymphoid cells with an occasional mononuclear giant cell and a fairly liberal sprinkling of multinuclear cells of the myeloid type. The veins in the medulla of the the suprarenal capsule were thickened, and in their walls were collections of small round cells and, rarely, a multinuclear giant cell. In the interstitial tissues of the adrenal were irregularly outlined collections of small round cells of the lymphocytic type, but among them giant cells were not to be seen.

Comment. Comment on this case, which represents a new phase in the pathology of Hodgkin's disease, is reserved for that section which deals with the changes in the liver as a whole.



FIG. 3.—Case VIII. Photomicrograph of a thickened vein in the substance of the spleen. In the walls of the vein are collections of lymphocytes and numbers of atypical giant cells.

CASE IX. Predominant Enlargement of the Spleen in Hodgkin's Disease.—The patient, R. H., female, aged sixty years, was admitted to Bellevue Hospital, May 21, 1913, and died June 5, 1913. There is nothing in the clinical history of importance in the present connection, with the possible exception that the patient stated that two years previous to admission she had suffered from an attack of "malaria." At the time of admission she complained of shortness of breath on exertion, weakness and loss of weight. The temperature showed no noteworthy deviations from the normal.

Autopsy Findings. The body was that of a poorly nourished, elderly female. The skin presented a slightly bronzed appearance. There were palpably enlarged lymph nodes in the axillary, supraclavicular and inguinal regions, all of them firm, discrete and freely movable. The lower border of the liver lay on a level with the crest of the ilium. Both pleural cavities were distended by clear straw-colored fluid. In the lower lobe of the left lung, near the anterior and inferior margin, was a solitary nodule, 3 cm. in diameter, grayish-white in color. The peribronchial lymph nodes were noticeably enlarged, firm and, on section, presented a fleshy appearance. The visceral pericardium and the epicardial fat contained numbers of small, firm, grayish-white, nodular foci. The spleen was firm and greatly enlarged, weighing 657 gm. and measuring 19 by 12½ by 5 cm. On section the cut-surface presented numerous small yellowish foci. The liver was increased in size, measuring 27 by 25 by 7 cm. and weighing 2470 gm.

Histology. Microscopical examination of lymph nodes from various parts of the body showed diffuse hyperplasia of lymphoid cells, large numbers of multinuclear giant cells and of large mononuclear forms and a few eosinophiles, the whole supported by a fibroblastic reticulum. The spleen showed extensive replacement by connective tissue, scattered through which were relatively small numbers of lymphocytes, an occasional large mononuclear cell and, rarely, a myeloid giant cell. At intervals were richly cellular collections of lymphocytes, among which were conspicuous numbers of myeloid giant cells, large mononuclear forms and an occasional eosinophile. The nodule in the lung showed a fibroblastic connective tissue frame work in which were islands composed of lymphocytes with a few myeloid giant cells and large mononuclear forms. Eosinophiles were evident in small numbers. The nodules in the epicardium showed innumerable lymphocytes, considerable numbers of eosinophiles and moderate numbers of mononuclear giant cells and an occasional multinuclear cell of the myeloid type. In the perilobular spaces of the liver were large and small, irregularly outlined collections of lymphocytes, among which myeloid giant cells and large mononuclear forms were occasionally to be seen. In many places the cellular foci lay in a sclerotic reticulum; in other places the periportal connective tissues were converted into rounded or streak-like masses of hyaline material in which few, if any, cells were discernible.

Comment. Whether there is a form of Hodgkin's disease that is "primary" in the spleen has been questioned—I refer to enlargement of the spleen without involvement of the lymph nodes, or in connection with which it can be shown with reasonable certainty that involvement of the lymph nodes, when present, is secondary to enlargement of the spleen.

In 1909 I described the case of a girl, aged eighteen years, who, for a period of three years before admission to the hospital, knew that there was a mass in the left side of her abdomen.⁴ Four months before entering the hospital she experienced irregularly recurring chills alternating with fever, sometimes two or three times in the course of the day. The edge of the spleen was felt $2\frac{1}{2}$ cm. above Poupart's ligament on the left side, whence it could be traced 6 cm. to the right of the umbilicus and thence upward to the ensiform cartilage. No superficial lymph-node enlargements were present. The spleen, which was removed by operation, measured 25 by 18 by 8 cm. and, upon microscopical examination, presented the histology of Hodgkin's disease. At the time of operation no enlarged lymph nodes were seen or felt in the abdomen. Death occurred, but necropsy was not obtainable.

Four years later Wade⁵ described the case of a man, aged fifty-five years, a resident of Louisiana, who complained of intermittent chills, fever and sweats, and enlargement of the spleen, surgical removal and microscopical examination of which showed the histological picture of Hodgkin's disease. In his case there were no superficial lymph-node enlargements, nor were enlarged abdominal nodes noted at the time of operation. No autopsy was obtained.

Three years after this Mellon⁶ described the case of a girl, aged seventeen years, who, for eight months, had complained of severe pain in the left hypochondriac region and of intermittent chills and fever. The spleen was removed surgically, and microscopical examination showed the histology of Hodgkin's disease. The spleen is described as "enlarged," but its measurements and weight are not given. Mellon's description is equally vague as to the size and number of the lymph-node enlargements as revealed by necropsy, although he states that the cervical nodes were not enlarged and indicates that the inguinal nodes were only slightly enlarged. Microscopical examination of nodes removed from the chest, abdomen and inguinal region showed the histology of Hodgkin's disease. His report is too indefinite to be accepted unequivocally as an example of predominant Hodgkin's disease of the spleen with secondary lymph-node enlargement.

Cases of the type described by myself and later by Wade and Mellon, and again by myself in this paper, indicate the probable existence of a variety of Hodgkin's disease in which the lymphoid follicles in the spleen are involved to such an extent as to bring about massive enlargement of the organ, while the lymph-node enlargements are relatively insignificant. There can be no question that in certain cases there is a phase *in the clinical evolution* of Hodgkin's disease that is marked by enlargement of the spleen before the appearance of recognizable signs of involvement of the lymph nodes of the neck, chest or abdomen. In addition to the

evidence just submitted it may be mentioned that at the time of the present writing (January, 1923) there is a patient in Bellevue Hospital whose spleen reaches into the pelvis and as far forward as the mammillary line. She was under observation for several weeks with the enlarged spleen as the only clinically detectable sign of disease. Finally, a small solitary lymph node appeared in one of the anterior cervical triangles. It was removed, and microscopical examination showed the histological changes of Hodgkin's disease.

It is to be noted that several of the patients above referred to gave a history of intermittent chills and fever. This is of significance in connection with the well-recognized form of disease originally described by Murchison,⁷ and since him by investigators in different parts of the world, among others by Pel⁸ and by Ebstein,⁹ under whose names it is all too often compounded in the annals of patronymic medicine. The syndrome of Murchison is characterized by enlargement of the spleen with or, as has been claimed, without enlargement of the lymph nodes, the histological changes in the spleen and in the lymph nodes disclosing the characteristic features of Hodgkin's disease. The condition is apt to be protracted over a term of one or two years and, among other things, is attended by periods of intermittent pyrexia lasting for two weeks or longer, in the intervals between which the patient feels perfectly well and is kept in bed only with difficulty.

CASE X. The Association of Hodgkin's Disease with Pigmentation of the Skin Resembling Acanthosis Nigricans.—J. N., aged thirty-five years, was admitted to Bellevue Hospital, November 1, 1922, and died December 13, 1922. The patient stated that about three months previous to admission he had "caught cold," after which he began to lose weight. On September 15, 1922, he noticed that his mouth was sore and that there was an eruption throughout the buccal mucous membrane and on the lips, and that the tongue was covered with whitish material. The patient likened the appearance of the mucous membrane of his mouth to "white boiled skin." This condition lasted three days and was followed by desquamation, leaving the mouth in an apparently normal condition. At the same time the patient noticed a "rash" on the face that spread to the neck and, at the end of about four days, had involved the entire body. According to his description, the rash was accompanied by papules which oozed watery serum, dried and fell off, leaving pigmented macules. The rash was attended by a sensation of tingling, but there was no itching. The rash disappeared from the face, but persisted over the rest of the body. At the time of the appearance of the rash in the skin and the sore mouth the patient noticed for the first time that there was swelling of the nodes on both sides of the neck, and that he felt feverish

and weak. The patient's account of the changes in his mouth and skin was substantially confirmed by his physician, Dr. Masoni, who also stated that the patient's temperature at the time varied between 102 and 104° F. A year before coming to Bellevue, however, the patient was admitted to Mount Sinai Hospital, where it is recorded, according to information courteously sent to us by the Superintendent of the hospital, that the cervical lymph nodes on the left side were enlarged. Two weeks before admission to Bellevue Hospital the patient began to have dull pains in the lumbar region and across the chest, the latter accentuated by deep inspiration. At the time of admission he also complained of pain in the abdomen, nausea, shortness of breath, loss of 40 pounds in weight, weakness and a rash on the body.

Physical Examination. No pigmentary or other changes in the mouth. Numbers of enlarged, discrete, movable nodes were felt on both sides of the neck, just above the clavicles. In both axillæ the lymph nodes were markedly enlarged and discrete. The skin was roughened and presented diffuse brownish pigmentation, involving practically the whole of the body. The face was not affected. Scattered through the skin were numbers of rounded, brownish, circumscribed macules which varied in size from 2 to 5 mm. The chest showed diminished expansion on the right side and dulness over the entire right upper lobe, attended by diminished tactile fremitus, broncho-vesicular breathing, with prolonged, harsh, hissing expiration and many moist rales at the end of inspiration. The voice sounds over this area were increased almost to bronchophony. There was dulness over the manubrium. The heart sounds were muffled. The liver was palpable 9 cm. below the ensiform and was tender. The spleen was greatly enlarged, tender and firm, reaching to the level of the umbilicus; it was palpable over an area 8 by 12 cm. A lymph node removed from the neck and submitted to histological examination showed the characteristic lesions of Hodgkin's disease. The nodes of the abdomen, chest and neck were subjected to roentgen-ray therapy on seven occasions. Blood count showed 3,800,000 red cells, 70 per cent hemoglobin; 16,200 leukocytes, of which 92 per cent were polymorphonuclear neutrophils, 7 per cent lymphocytes and 1 per cent eosinophiles. Wassermann reaction was negative. Blood-pressure was 98/78.

Autopsy Findings. Hodgkin's disease, with massive enlargement of the thoracic and abdominal lymph nodes; moderate hyperplasia of the axillary and cervical groups; massive splenomegaly with multiple granulomatous foci; innumerable minute whitish foci in liver; small whitish focus in left kidney; multiple nodules in epicardial fat; massive thickening of pleura of upper lobe of right lung (Hodgkin's disease of the pleura); chronic interstitial pneumonitis of upper lobes of both lungs; multiple patches of miliary

tubercles in both lungs; fibrosis of peribronchial nodes on right side; bilateral hydrothorax; extensive brownish pigmentation of skin with numerous brownish black macules (acanthosis nigricans?).

Histology. The most striking feature in the histology of lymph nodes removed from various parts of the body was the extent to which they had been replaced by connective tissue. In some of them sclerosis had occurred in such manner as almost completely to convert the node into a solid fibrous mass, scattered through which were a few lymphocytes and considerable numbers of mononuclear and multinuclear giant cells. In other places the lymph nodes were more cellular and presented moderate numbers of lymphocytes, large numbers of mononuclear giant cells, many of them with pale, poorly chromatic nuclei, others richly chromatic; and a liberal supply of multinuclear myeloid giant cells and small numbers of eosinophiles and eosinophilic myelocytes. In the peribronchial nodes sclerotic areas supporting lymphocytes and mononuclear and multinuclear giant cells were found side by side with epithelioid tubercles, some of the latter presenting central areas of caseation. The pleura covering the upper lobe of the right lung was converted into dense, hyaline connective tissue with scattered islands of lymphocytes, eosinophiles and eosinophilic myelocytes, mononuclear and multinuclear giant cells. The underlying lung tissue presented numbers of sclerotic bands, in the intervals between which were alveolar remnants, an occasional embryonal alveolus and scattered collections of lymphocytes and mononuclear and multinuclear giant cells. Examination of tissue removed from other parts of the lung showed numerous interstitial epithelioid tubercles. The spleen contained innumerable whorl-like collections of fibroblastic connective tissue, imbedded in which were large numbers of mononuclear and multinuclear giant cells and a few eosinophiles and eosinophilic myelocytes. The nodules in the epicardial fat revealed histological changes identical with those in the lymph nodes. Sections of the skin showed innumerable minute brownish or brownish-black pigment granules in the lowermost layers. The epithelial covering was atrophic. The suprarenal capsules were intact. The liver contained numbers of interstitial epithelioid tubercles.

Comment. In this patient the occurrence of asthenia, low blood-pressure, nausea and muffled heart sounds, together with diffuse bronzing of the skin and localized spots of darker color suggested Addison's disease, due to destruction of the adrenals and the celiac ganglia by pressure from enlarged lymph nodes in the abdomen. At necropsy the adrenals were found to be intact and there was no pigmentation of mucous membranes observed during life or at necropsy. The celiac ganglia could not be identified and were probably submerged in the masses of enlarged nodes that lay in the immediate vicinity of the adrenals. On the other hand, the

changes in the skin bore a certain resemblance to those encountered in the so-called *acanthosis nigricans*—a condition described independently by Pollitzer¹⁰ and Janovský in 1891, and since then recognized as a clinical entity by observers in various parts of the world. It is characterized by widespread pigmentation of the skin and by pigmented verrucosities or macules and, in certain cases, by papillary hypertrophy of the mucous membrane of the mouth, without pigmentation. The cutaneous changes are usually symmetrical and affect principally the axillæ, neck, the external genitals, the groin, the inner aspect of the thighs, the back of the hands, the flexor surfaces of the elbows and knees and, occasionally, the eyelids. Two types are recognized—an adult and a juvenile—and between them are certain noteworthy differences. The juvenile form pursues a benign course and may be prolonged over years without detriment to the general health of the patient. The adult form, on the other hand, is usually fatal within a year or two and is attended by marked disturbances of health, and appears to represent the cutaneous expression of disease in the deeper parts. In 35 cases of the adult variety of *acanthosis nigricans* collected by Pollitzer and published in 1909¹⁰ 21, or 60 per cent, were investigated at necropsy, and in all of them malignant growths were found in the abdomen or pelvis. In 14 cases the alimentary tract was the seat of carcinoma, in 5 cases the uterus was involved and in 2 cases the structures in the abdomen were metastasized from primary carcinomata in the breast. In an additional 6 cases there was strongly presumptive clinical evidence of malignant growths in the abdomen, but confirmation by necropsy was not obtained. Pollitzer subscribes to the theory originally advanced by Darier, that the adult form of *acanthosis nigricans* is due to interference with the functions of the abdominal sympathetic system, brought about by pressure from malignant growths. In the case here recorded this interpretation appears to be applicable to the changes in the skin, since the regions normally occupied by the sympathetic system, including the celiac ganglia and the paraganglia, were invaded by nodular masses which, although they represented the hyperplastic lymph nodes of Hodgkin's disease, appeared no less effectually to bring about disturbances in the sympathetic system, manifested by pigmentary disturbances in the skin of the same type as those encountered in Addison's disease and in *acanthosis nigricans*, and yet conforming strictly to neither, either clinically or anatomically. This case is furthermore interesting as illustrating the association of Hodgkin's disease and epithelioid tubercles, sometimes in the same microscopical field.

(To be continued.)

TUBERCULOSIS AS AN ETIOLOGICAL FACTOR IN HODGKIN'S DISEASE: A HISTORICAL REVIEW.¹

BY WILLIS S. LEMON, M.B. (TOR.),

SECTION ON MEDICINE, MAYO CLINIC, ROCHESTER, MINN.

AFTER Hodgkin's first description of the disease that later was to bear his name, no interest was excited until Wilks, in England, and Bonfils, in France, reported similar cases twenty years later. Neither of these men knew of the other's work and each seemed in ignorance of Hodgkin's original article; Wilks, in fact, used museum specimens that had been described by Hodgkin from the cases of Morgan (J. S., aged nine years), Bright (E. K., aged ten years) and Addison (T. W., aged fifty years). The following ten years were more productive, and case reports were written by Wunderlich, Pavy and Potain, and in 1865 a second report by Wilks appeared, in which the disease was recognized as an entity and the name "Hodgkin's disease" suggested.

In spite of the confusion always existing under such circumstances, the clinical details had been very well worked out, and Wilks, Trousseau and Wunderlich had differentiated the disease from leukemia, syphilis, malignant forms of lymphosarcoma and tuberculosis. This Hodgkin had failed to do, and in his description had included such diseases, especially tuberculosis and syphilis. The disease was regarded as a variety of lymph-gland tumor, associated with splenomegaly and an enlarged liver, and accompanied by anemia, fever and progressive loss in vitality.

Hodgkin's own description of the clinical findings and his speculation as to the cause of the disease cannot better be described than by quoting from his paper: "As far as could be ascertained from observation, or from what could be collected from the history of the cases, the enlargement of the glands appeared to be a primitive affection of these bodies rather than the result of an irritation propagated to them from some ulcerated surface or other inflamed textures through the medium of their inferent vessels, and that although in some instances the glands so enlarged may contain a little concrete inorganizable matter, such as is known to result from what is called scrofulous inflammation, it is obvious that this circumstance is not an essential character, but rather an accidental and concomitant to the idiopathic interstitial enlargement of the absorbent glandular structure throughout the body. That unless the word inflammation be allowed to have a more indefinite and loose meaning than is generally assigned to it, this affection of the glands can scarcely be attributed to that cause, since they are

¹ Read before the Muncie Academy of Medicine, Muncie, Indiana, May, 1923.

unattended with pain, heat and other ordinary symptoms of inflammation, and are not necessarily accompanied by any alteration in the cellular or other surrounding structure, and do not show any disposition to go on to the production of pus or any other acknowledged product of inflammation except where, as in the cases above alluded to, inflammation may have supervened as an accidental affection of the hypertrophied structure. . . . Notwithstanding the different characters which this enlargement may present, it appears nearly in all cases to consist of a pretty uniform texture throughout, and this rather to be the consequence of a general increase of every part of the gland than of a new structure developed within it, and pushing the original structure aside, as when ordinary tuberculous matter is deposited in these bodies. At the same time it must be admitted that the new material by which the enlargement is affected presents various degrees of organizability, which in some instances is extremely slight, and appears incompetent to maintain the vitality of the affected gland."

Malpighi was of the opinion that the involvement of the spleen, with its characteristic island of lymphoid material resembling miliary tubercles, was associated with the glandular affection but might appear later in the course of the disease. He explained the absence of splenic disease by assuming that death might occur from the ravages of the disease before the onset of pathological changes within that organ.

Wilks, in his first paper, in considering lardaceous disease and its allied affections, makes a division into different classes. In his Class V are cases of a peculiar enlargement of the lymphatic glands often associated with diseases of the spleen. He subdivides Class V into two groups: (1) cases associated with lardaceous disease and tuberculous affections; and (2) those with a peculiar disease of the spleen, appearing to constitute a special form of malady.

We give credit to Markham, who reported a similar condition, and in the speculation regarding its cause, remarks: "There was little evidence to show that they were malignant and not stronger than they were scrofulous."

Wilks also quotes *verbatim* Bright's description of the various forms of the disease displayed by the spleen and of one variety which seems to be identical with that referred to by Hodgkin. Bright, however classifies the disease as malignant, and says: "There is another form of disease which appears to be of a malignant character, though it varies from the more usual form of malignant disease, and which has been particularly pointed out by Dr. Hodgkin as connected with extreme disease of the absorbent glands, more particularly those which accompany the bloodvessels. The whole of these absorbent glands become larger and firmer, without any tendency to suppurate, as in ordinary scrofulous disease, or to soften, as in cerebriform disease; at the same time, the spleen

becomes more or less completely infiltrated through its whole substance with a white matter, with almost the appearance of suet. This matter insinuates itself into the cellular structure of the spleen, but it is no easy matter to point out what particular portion of the structure receives it. A section of the organ seems to show, from the irregular forms assumed, that it fills a cellular structure, and in some degree takes its shape from the cells into which it enters, having less tendency to assume the form of regular globular masses or tubera than other malignant disease."

Wilks, on the other hand, describes in minute detail not only the progress of the disease, but also its differentiation from scrofula: "The enlargement of the glands is in most cases gradual, extending sometimes over a period of two, three or more years, and often, from commencing in the neck in tuberculous, weakly children, is called scrofulous. When the mischief is thus gradual in its commencement, and affecting only part of the glandular system, no marked symptoms ensue, but as time tends to its development in the thoracic and abdominal glands a slow prostration ensues, terminating in death. The glands often reach an enormous size, much larger than when affected with scrofula, a bunch of them often being composed of separate tumors, each the size of an egg. When felt during life, in their early progress, they are recognized by their peculiar elastic feel, differing both from the early hardness or the subsequent softness of scrofulous glands."

Following a very excellent description of the progressive development of the disease, both from its anatomical characteristics and constitutional effects, he concludes: "We have been content, therefore, with briefly stating the main facts connected with a particular class of disease, including several morbid conditions whose identity is not proved, but whose close relationship appeared to warrant the adoption of the present method of narration, in order to fix attention to them. First, there are the cases of simple lardaceous disease occurring alone; then those associated with tuberculosis; then those cases connected with disease of bone; afterward those found in connection with a peculiar affection of the glands; and, lastly, those cases where this latter condition of the glands occurred unassociated with lardaceous disease (unless white deposit in the spleen be a modification of it), but allied to the previous classes by a close relationship."

In Wilks' second paper, he says: "It is true that enlarged glands may be met with in various forms of disease, and sometimes with the lardaceous, and thus the two affections may have relationship; these would appear, also, to have a likeness to tubercle on the one hand, and cancer on the other. It is, however, as much a disease *sui generis* as any other and deserves a description of its own. . . . As regards its degree of malignancy, it appears to take a place between cancer and tubercle, the growth in the glands,

with implications of the bronchial tube and pulmonary tissue, resembling the former, while the mode of deposit in the splenic corpuscles and along the minute vessels of the portal system of the liver resembles tubercle.

"In this way this disease of Hodgkin is clearly separable from lardaceous disease, from cancer and tubercle, although all these affections may bear a relation to one another. Its association with tubercle is seen in the class of organs and the tissues affected, and even by the presence of deposit in the lungs, which may be in fact real tubercle."

Pavy noted, as suggestive of Hodgkin's disease, certain features which are accepted today, particularly the extreme pallor or anemia and the enlargement of one or more lymphatic glands, either internal or external, with enlargement of the spleen, and says: "The enlargement of the lymphatic glands, which thus seems the peculiar feature of this malady, is remarkable for the lingering form of fatal cachexia which it produces.

"It may gradually extend over a period of two or more years when the thoracic and abdominal glands become involved, and slow prostration precedes death."

In the early days the disease was known under many names, depending on the author's fancy, and these names are still in use and still cause confusion. On this phase Longcope and McAlpin say: "From the time of the first comprehensive description of this disease by Hodgkin, in 1832, the affection has been designated by a great variety of names, which, during the early history of the disease, led to considerable confusion. Most of these older terms, such as 'malignant lymphoma,' 'pseudoleukemia' and 'lymphadenoma,' have been relinquished, and the disease is now widely known as Hodgkin's disease. In Germany the name 'lymphomatosis granulomatosa' or 'lymphogranulomatosis' is employed. In England the term 'lymphadenoma' is still retained."

However, certain similarities began to be pointed out which showed the close relationship to tuberculosis. Hilton Fagge, in 1874, described a primary glandular tuberculosis that, clinically, could not be differentiated from Hodgkin's disease. In his case the glands were large, remained discrete, had no periglandular infiltration and appeared in the areas usually the site of Hodgkin's disease.

Ten years later Weigert described a case that apparently belonged to the pseudoleukemias, but on section showed evidence of tuberculosis or a bacillus resembling that of tuberculosis. Three years later Delafield made a similar observation, describing a primary glandular tuberculosis, and within the next few years many others noted the striking similarity in the two types of adenopathy.

Delafield's case was interesting because of the difficulty in diagnosis and the unusual character of the tuberculosis affecting the patient. He used Dr. Ball's description because it was indicative

of the difficulty of diagnosis. In the same description, Dr. Ball mentions the fact that typhoid fever could be early excluded and that general tuberculosis was considered, although no evidence was found except in the enlargement of the cervical lymph glands and in the spleen. These glands were hard, tender, freely movable, gradually increasing in number and associated with anemia. Later in the disease the axillaries and inguinals became involved. The possibilities finally were reduced to two: either tuberculosis confined to the glandular system or Hodgkin's disease in an acute form, the latter being more plausible because of the rarity of so restricted a form of tuberculosis. In his note, however, he reports cases of acute Hodgkin's disease described by Gowers and Hilton Fagge. He says in conclusion: "Some cases of this kind are described by the older authors under the name of acute scrofula. Others have been confounded with the morbid condition known under the names of Hodgkin's disease, pseudoleukemia, adenia, anemia lymphatica, lymphadenoma and malignant lymphoma. A few cases similar to the one here reported have been described by Hilton Fagge and Pye Smith."

Sternberg, in a long article, reviews the literature, and describes the studies on etiology, including many forms of organisms, that had been undertaken up to his day. He rejects these explanations of the etiology of the disease and concludes that Hodgkin's disease is a peculiar type of tuberculosis. Of his 13 cases of pseudoleukemia, 8 revealed the presence of tuberculosis in one or more organs, or the bacillus itself was found within the glands. This opinion was destined to have a very powerful influence on the later conception of the disease, an influence felt even to the present day. However, a number of his contemporaries, Weishaupt, Westphal, Dietrich and Fischer, modified his view somewhat; Westphal because the *Bacillus tuberculosis* was absent in most examinations and because inoculation experiments were failures in most cases. These authors were of the opinion that tuberculosis might be a factor, but that it appeared as a secondary invader.

Andrewes also refused to accept the Sternberg hypothesis, and offered as explanation for the presence of the *Bacillus tuberculosis* the belief that the lymphatic gland acts as a filter for bacteria. Therefore, the finding of tuberculosis bacilli in the gland proves only the germ's presence, not that the gland itself is tuberculous.

That the patient may have tubercular glands, but not be tuberculous, was shown by Pizzini, who used glands from necropsies of people who died from other diseases, and found 42 per cent positive for tuberculosis. Of the glands studied, the tracheo-bronchial glands gave the highest percentage of positives. Such a finding is in agreement with the experience of pathologists at the present time, and with the anatomical studies on tuberculosis of Ghon, in Germany, and of Opie, in this country.

In 1891 Northrup reached similar conclusions, finding tuberculosis limited to the bronchial lymph glands in 13 of 125 necropsies on tuberculous children who died of non-tuberculous diseases, and Holt, in 1903, reports having seen similar findings. Loomis, in a necropsy study of 30 persons who died from violence or acute disease, found 8 whose bronchial glands produced tuberculosis in inoculated animals, although in the patients there was no evidence of tuberculosis outside the glands.

Sailer, however, in 1902, thought the majority of cases were due to tuberculosis. He says: "That certain of the cases are due to a peculiar form of tuberculosis of the lymphatic apparatus has been recognized for a considerable length of time, chiefly as a result of the brilliant article of Sternberg; but such cases have been considered rather as pathological curiosities than as clinically recognizable. The majority of cases have been diagnosed pseudoleukemia, and only the necropsy has revealed the true condition. . . .

"That the glands in many instances contain tubercle bacilli is no longer a matter of question, and that these bacilli are capable of infecting susceptible animals has been conclusively proven. Moreover, it has been shown that in many cases with the characteristic histological picture of lymphoma, tuberculosis exists, and the tubercle bacilli may be numerous and virulent. It does not necessarily follow that they are the cause of pseudoleukemia, because, as many authors have suggested, they may exist either as a secondary or as an associated infection. That is to say, there is no reason why lymph glands, the seat of tuberculosis, might not take on the changes and produce the symptoms of a pseudoleukemia, or that lymph glands characterized by the morbid laterations of pseudoleukemia and associated with symptoms of that disease might not become infected with tubercle bacilli." We are in complete agreement with this last statement.

Another explanation for the presence of tuberculosis in the glands of patients with Hodgkin's disease was offered by Parkes Weber. He believed that lymphadenomatous tissue offered a soil favorable to the growth of tuberculosis bacilli, and that they were able to establish themselves and flourish in glands affected with Hodgkin's disease. Thus, children with Hodgkin's disease ultimately develop fatal disseminated miliary tuberculosis. In explaining his belief, he quotes Quincke's view that the development of tuberculosis in Hodgkin's disease sometimes causes retrogression of the lymphadenomatous process, as was observed in patients with leukemia who became tuberculous. The finding of tuberculosis bacilli therefore does not prove that the original disease may not have been lymphadenoma.

Further evidence of the distinctiveness of the two diseases appeared with the reports of Reed, Longcope and Simmons. In Reed's series of 8 cases of Hodgkin's disease, 1 patient died of

miliary tuberculosis. There was no tuberculosis in the other 7 cases, 5 of which came to operation, and 2 to necropsy. Two inoculation experiments also failed to produce tuberculosis. In Longcope's series of 8 cases tuberculosis was not found in any, although 4 came to necropsy, and 4 inoculation experiments were made.

In Simmons' 9 cases there were 5 negative inoculation experiments, and in Warnecki's 9 cases 4 negative inoculations; 1 patient, however, had apical tuberculosis.

On the other hand, Yamasaki found small foci of tuberculosis in bronchial glands, lung apices, or intestines in 4 of 6 necropsies. Such a report, however, must be considered in the light of the work of Ghon, Opie, Pizzini, Northrup and Loomis.

In 1914 Wuttke concluded that Hodgkin's disease is an infection due to a modified strain of tuberculosis bacilli, whose exact relation to the usual form has not yet been established. To support this contention, he quoted Mallory's definition given in a personal communication: "It is a name applied to a clinical condition. Some of the cases turn out to be tuberculosis; a few are cancer or other malignant tumors. The majority turn out to be lymphoblastoma." Wuttke also obtains support from O. Meyer and K. Meyer, who obtained the Much granule, repeatedly reproduced it in guinea pigs, and in their third case found tuberculosis; also from Heinz, who, using the antiformin method, found human tuberculosis; and from Löffelmann, who in 7 cases of Hodgkin's disease observed positive tuberculosis in 6 and the Much granule in 1. Errors may have crept in because of technical difficulties. It is possible that the peculiar cultural and staining reactions of such organisms may be explained as suggested by Gaarde, who said: "The diphtheroid bacillus obtained in the culture of Hodgkin's glands, when grown in egg-yolk media which contains fat, sometimes has a tendency to become acid-fast when stained with carbol fuchsin. Unlike tubercle bacilli, they are rather easily destained, yet are much more resistant to destaining with acid alcohol than the common bacteria."

As late as 1921 Loygue states that the etiology is uncertain, but in the absence of any proof of any specific cause for Hodgkin's disease, a tuberculous origin would seem to be the most likely.

Symmers considers that both the tuberculous and the diphtheroid organism theory have failed of confirmation, and defines his conception of the nature of the disease as follows: "Hodgkin's disease is neither infectious nor neoplastic, but a systemic disease expressing a predilection for lymphoid tissue, giving rise to multiple foci of growth at approximately the same time in response to the same provocative agent."

Clinical Similarity of the Adenopathy in Tuberculosis and in Hodgkin's Disease. When a patient with adenopathy appears for diagnosis the examiner must consider the possibility of Hodgkin's disease, lymphosarcoma, lymphatic leukemia, syphilitic adenopathy,

true malignancies (either carcinoma or sarcoma) and tuberculosis, in making a differential diagnosis. Many times the clinical examination is insufficient, and a biopsy must be made before a diagnosis can be obtained. One of the most clinically characteristic cases of Hodgkin's disease that has come to my attention proved on blood examination and biopsy to be lymphatic leukemia. Yet the distribution of the adenopathy, the progress of the disease and the presence of pruritus were characteristically those of Hodgkin's disease. Of 191 patients, either seen personally or whose records have been available to me for study, tuberculosis of the glands had to be taken into account in a considerable number. This was especially true in a case of Hodgkin's disease which gave evidence of marked tenderness on palpation of the glands. I believe that difficulty in differentiating tuberculosis and Hodgkin's disease is a common experience of examiners. Longcope says: "Of all types of glandular enlargement, the one most often mistaken for Hodgkin's disease is tuberculosis. Sometimes indeed, from a clinical examination alone, it is impossible to tell the affections apart."

In my series a differential diagnosis from lymphosarcoma has proved the most difficult. Often the pathologist's report must be obtained before a decision can be reached. It has been my experience that such a report on one examination of tissue may be reversed at a later time when another gland is examined, and MacCarty is of the opinion that the lymphosarcoma and Hodgkin's disease may be but different manifestations of the same condition. Certainly this seems true from a consideration of the progress of the disease.

The similarity to tuberculosis applies to three types of that disease: (1) An acute, comparatively rare form in which the glands swell rapidly, appear on both sides of the neck (beginning in the nodes beneath the jaw and in the anterior triangle) are painful, tender to touch and associated with fever. These glands are regular, oval, firm but elastic, remain discrete, and on section reveal shiny raised points which are in fact typical miliary tubercles (Longcope). (2) The disease as described by Delafield and Fagge may exactly simulate Hodgkin's. In this type the tumors may be large and hard, appear in all gland-bearing areas, often remain discrete and without evidence of periadenitis, and yet on removal are found to be entirely caseous. (3) Patten and Bissel have reported a peculiar adenopathy occurring in negroes, which resembles in course and clinical features various types of glandular involvement, but more especially the leukemias, and which eventually proves to be tubercular. Nearly all the lymph glands are involved, but there is little or late involvement of the internal organs. The glands are elastic, smooth, ovoid or globular, unattached, painless, and are not tender, nor does suppuration occur. They are lobulated, as in Hodgkin's disease, and are associated with slow or rapid cachexia, continuous or irregular fever and increasing anemia.

There is usually no confusion regarding the typical tuberculous adenopathy with its caseation, suppuration and sinus formation, but 1 case of Hodgkin's disease was observed in my service that appeared as a large phlegmon of the neck associated with suppuration and multiple sinuses, in which the diagnosis of Hodgkin's disease was made by biopsy on the gland.

Pathology. Adami, in his discussion of tumors originating from tissue-producing lymphocytes, divided them into seven classes: (1) Chronic hyperplasia, of which some of the best examples are seen in connection with two forms of tuberculosis: (a) Specific granulomatous changes with caseation; (b) diffuse enlargement without caseation, but revealing fibrosis, increase of endothelial elements, and decrease of lymphatic elements (the paratuberculous lymphadenitis which is an overgrowth response to the stimulus of tissue). (2) Hodgkin's disease, in which an unknown irritant produces the hyperplasia; the marked feature is the reticular and connective-tissue overgrowth similar to what is noticed in the tuberculosis group. (3) A type of gland resembling Hodgkin's disease microscopically, but on intensive staining, showing the *Bacillus tuberculosis*, the granulomatous hyperplastic lymphadenitis of Ewing. (4) Leukemia, an overgrowth of otherwise normal lymphadenoid tissue, and a passage into the blood of large numbers of lymphocytes. (5) Typical lymphoma. (6) Lymphosarcoma. (7) Lymphosarcomatosis. Such a conception permits of borderline types that may be difficult of classification, either from the clinical or the pathological viewpoint.

When the pathological picture was made definite by Reed, Longcope and Simmons, their description of the first stage was remarkably similar to that of an inflammatory state. They described the hyperplasia of the lymphoid cells with active proliferation in the germinal centers, the increase in vascularity, the proliferation of reticular endothelium, the dilatation of the lymph sinuses which are crowded with lymphocytes, both small and large, polymorphonuclear leukocytes, eosinophiles and endothelial cells, a description not unlike that of early inflammation. A node due to an early first stage of Hodgkin's disease is very difficult to differentiate from the hyperplastic lymph node of toxemia, or the inflammatory reaction, or from lymphatic leukemia. In the late stage of Hodgkin's disease, confusion is possible because of the presence of fibrosis, accumulation of lymphocytes and Reed giant cells, that may simulate the Langhans cell of tuberculosis.

Clinical Observations at the Mayo Clinic. In October, 1921, Doyle and I became interested especially in the mediastinal involvement of Hodgkin's disease, and inquired into the history of such patients in order to determine how often tuberculosis was an etiological factor, or an associated disease. Of more than 26 cases, in which mediastinal involvement was observed, only 2 knew of tuberculosis in the family; 1 of these reported that a cousin had had tuber-

culosis of the cervical glands, and another believed that a maternal aunt had died of pulmonary tuberculosis. Roentgen-ray examination revealed evidence of tuberculosis in only 1 patient, and this finding could not be confirmed by clinical or microscopical examination. Moreover, at necropsy no evidence of tuberculosis was found in 3 instances.

In only 1 other case which I have observed was tuberculosis clinically evident during the course of the disease. This case was not included among the 26 because there was no clinical evidence of mediastinal involvement.

A summary of 191 cases of Hodgkin's disease was recently made, and in only 8 was there evidence of tuberculosis. This evidence was seen in roentgenograms of the chest. However, in a review of 191 unselected routine cases comprising many different diseases, the roentgenograms of the chest revealed evidence of 17 cases of tuberculosis in either healed or open form. This would seem to indicate that tuberculous involvement of the mediastinum is not as common a complication in Hodgkin's disease, as in other diseases, but in making such a comparison one must keep in mind the infrequency of pulmonary tuberculosis in cases of glandular involvement with that disease.

Conclusion. There are many similarities between tuberculous adenopathy and that of Hodgkin's disease, which are often very confusing to the clinician, and occasionally to the pathologist, but I believe that infection with tuberculosis bacilli does not produce Hodgkin's disease, although the two diseases may be associated.

BIBLIOGRAPHY.

1. Adami, J. G.: Principles of Pathology, 2 ed. Philadelphia, Lea & Febiger, 1910, 1, 739.
2. Andrewes, F. W.: Discussion of Lymphadenoma in its Relation to Tuberculosis, Tr. Path. Soc., London, 1902, 53, 305.
3. Bonfils, E. A.: Quelques réflexions sur un cas d'hypertrophie ganglionnaire générale; avec fistules lymphatiques et avec cachexie, sans leucémie, Rec. de trav. Soc. méd. d'obs. de Par., 1857-1858, 1, 157.
4. Delafield, F.: A Case of Acute and Fatal Tuberculosis of the Lymphatic Glands, Med. Rec., 1887, 31, 425.
5. Dietrich, A.: Ueber die Beziehungen der malignen Lymphome zur Tuberkulose, Beitr. z. klin. Chir., 1896, 16, 377.
6. Ewing, J.: Neoplastic Diseases; a Treatise on Tumors, 2 ed. Philadelphia and London, W. B. Saunders Company, 1922.
7. Fagge, H.: A Case of Progressive Caseous, and Probably Tubercular, Disease of the Lymphatic Glands and Spleen, Path. Tr., 1874, 25, 235.
8. Fischer, F.: Ueber malignes Lymphon, Arch. f. klin. Chir., 1897, 55, 467.
9. Fraenkel, E. and Much, H.: Bemerkungen zur Aetiologie der Hodgkinschen Krankheit und der Leukemia lymphatica, Muenchen. med. Wehnschr., 1910, 57, 685.
10. Gaarde, F. W.: Personal communication.
11. Ghon, A.: The Primary Lung Focus of Tuberculosis in Children, ed. (Eng.), authorized transl. by D. Barty King, New York, Paul B. Hoeber, 1916.
12. Heinz, E.: Ein Beitrag zu Lehre von der Lymphogranulomatosis, Frankfurter Ztschr. f. Path., 1912, 10, 383.
13. Hodgkin: On Some Morbid Appearances of the Absorbent Glands and Spleen, Med. Chir. Tr., 1832, 17, 68.
14. Holt, L. E.: The Diseases of Infancy and Childhood, 1 ed. New York, D. Appleton & Company, 1904.

15. Lemon, W. S. and Doyle, J. B.: Clinical Observations of Hodgkin's Disease, with Special Reference to Mediastinal Involvement, *Am. Jour. Med. Sci.*, 1921, 162, 516.
16. Löffelman, H.: Ueber Befunde bei Morbus Hodgkin mittelst der Antiforminmethode, *Beitr. z. Klin. d. Tuberkulose*, 1912, 24, 367.
17. Longcope, W. T. and McAlpin: On the Pathological Histology of Hodgkin's Disease, with a Report of a Series of Cases, *Bull. Ayer Clin. Lab. Penn. Hosp., Phila.*, 1903-1904, 1, 14.
18. Loomis, H. P.: Some Facts in the Etiology of Tuberculosis Evidenced by Thirty Autopsies and Experiments upon Animals, *Med. Rec.*, 1890, 38, 689.
19. Loygue, G.: Contribution à l'étude de la maladie de Hodgkin, *Arch. d. mal. du coeur*, 1921, 14, 346.
20. MacCarty, W. C.: Personal communication.
21. Mallory, F. B.: Quoted by Wuttke as personal communication.
22. Meyer, O. and Meyer, K.: Zur Aetiologie des malignen Granuloms, *Berl. klin. Wchnschr.*, 1912, 11, 1463.
23. Northrup, W. P.: Tuberculosis in Children, *New York Med. Jour.*, 1891, 53, 201.
24. Opie, E. L.: The Focal Pulmonary Tuberculosis of Children and Adults, *Jour. Exper. Med.*, 1917, 25, 856.
25. Opie, E. L.: The Relation of Apical Tuberculosis of Adults to the Focal Tuberculosis of Children, *Jour. Exper. Med.*, 1917, 26, 263.
26. Patten, J. M. and Bissel, W. W.: Lymphatic Tuberculosis Simulating Hodgkin's Disease, *Chicago, Med. Recorder*, 1914, 36, 539.
27. Pavy: Case of Anemia Lymphatica, a New Disease Characterized by Enlargement of Lymphatic Glands and Spleen, *Lancet*, 1859, 2, 213.
28. Pizzini, D. L.: Tuberkelbacillen in den Lymphdrüsen nicht tuberkulöser, *Ztschr. f. klin. Med.*, 1892, 21, 329.
29. Potain, M.: Double tumeur lacrymale, engorgement lymphatique sous-maxillaire considerable, *Bull. Soc. anat. de Par.*, 1861, 6, 217.
30. Quincke, H.: Leukämie und Miliartuberkulose, *Deutsch. Arch. f. klin. Med.*, 1902, 74, 445.
31. Reed, Dorothy M.: On the Pathological Changes in Hodgkin's Disease, with Especial Reference to its Relation to Tuberculosis, *Johns Hopkins Hosp. Rep.*, 1902, 10, 133.
32. Sailer, J.: The Relation of the Tubercle Bacillus to Pseudoleukemia (Sternberg's Disease), *Philadelphia Med. Jour.*, 1902, 9, 615.
33. Simmons, C. C.: Hodgkin's Disease, a Pathological Analysis of Nine Cases, *Jour. Med. Res.*, 1903, 9, 378.
34. Sternberg, C.: Universelle Primärerkrankungen des lymphatischen Apparates *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1899, 2, 641; 770; 813.
35. Sternberg, C.: Ueber eine eigenartige, unter dem Bilde der Pseudoleukämie, *Ztschr. f. Heilk.*, 1898, 19, 21.
36. Symmers, D.: A New Interpretation of the Pathological Histology of Hodgkin's Disease, *Arch. Int. Med.*, 1917, 19, 990.
37. Trousseau: Quoted by Sternberg.
38. Warnecki, F.: Ueber die Hodgkinsche Krankheit, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1904, 14, 275.
39. Weber, F. P.: Acute Cases of Hodgkin's Disease (Lymphadenoma), *St. Barth. Hosp. Rep.*, 1907, 43, 81.
40. Weigert: Quoted by Cunningham, W. F.: The Status of Diphtheroids with Special Reference to Hodgkin's Disease, *Am. Jour. Med. Sci.*, 1917, 153, 406.
41. Weishaupt, H.: Ueber des Verhältniss von Pseudoleukämie und Tuberkulose, *Braunschweig, Appelhaus and Pfennigstorff*, pp. 31.
42. Westphal, A.: Beitrag zur Kenntniss der Pseudoleukämie, *Deutsch. Arch. f. klin. Med.*, 1892-1893, 51, 83.
43. Wilks, S.: Cases of Enlargement of the Lymphatic Glands and Spleen (Hodgkin's Disease), *Guy's Hosp. Rep.*, 1865, 11, 3s, 56.
44. Wunderlich, C. A.: Zwei Fälle von progressiven multiplen Lymphdrüsenhypertrophien, *Arch. f. physiol. Heilk.*, 1858, 2, 123.
45. Wuttke, E. E.: Hodgkin's Disease. Its Etiology and Pathology; Recent Investigation in its Relation to Tuberculosis, *Jour. Iowa State Med. Soc.*, 1914, 3, 117.
46. Yamasaki, M.: Zur Kenntniss der Hodgkinschen Krankheit und ihres Ueberganges in Sarkoma, *Ztschr. f. Heilk.*, 1904, 25, 269.

**MANAGEMENT OF THE DIABETIC PATIENT, WITH ESPECIAL
REFERENCE TO THE ADMINISTRATION OF INSULIN.**

BY WILLARD C. STONER, M.D.,

CLEVELAND, OHIO.

THE advances made in the problem of diabetes in the last ten years have given us a rational and satisfactory treatment of the disease. Previous to the work of Allen, in which he emphasized the importance of undernutrition in managing these cases, there was no satisfactory standardized treatment. The management consisted largely of the use and obviously abuse of drug therapy which was instituted without rhyme or reason. And while it is true that considerable attention was given to dietary management no satisfactory dietary regimen was uniformly practised even in our large clinics, and notwithstanding criticism that undernutrition treatment of disease is not treatment, the work of Allen must stand as the important background of our dietary management.

The work done on depancreatized animals by Minkowski and von Mering was confirmed by Allen and thus the absolute pathological change as being limited the pancreas was definitely established.

The work of Banting and his co-workers have given us a specific serum, insulin, which is a most valuable adjunct in the treatment of these cases, however, the observations to date do not indicate that the administration of insulin can in any way replace dietary management. There are certain fundamental facts in the management of the disease that are not generally known. It has been my observation that it is not common knowledge that alkalis are contraindicated in the routine management unless it be in coma, and then of rather limited value; that there is not a single drug that has value in treatment except as indicated for coexisting conditions that arise, such as failing myocardium in coma where digitalis may be indicated.

Blood-sugar estimations have become a routine in most hospital clinics and the necessity for these estimations in the management of these cases should be understood. It is important to do blood-sugar estimation to determine blood-sugar level and kidney threshold. It is important to do blood-sugar estimations to differentiate renal diabetes and glycosurias from diabetes mellitus. And while the writer does routine blood-sugar estimations at intervals on all diabetics whether insulin is administered or not, I do not believe it is a necessity for the satisfactory management of these cases. Blood-sugar level is an everchanging factor and as Newburg has pointed out that unless one has repeated observations in the twenty-four hour period, determinations do not represent the true level. Observation has shown that blood-sugar level in normal individuals

is at variance, and while we consider 100 mg. to 125 mg. per 100 cc of blood taken in the morning after no food for ten or twelve hours as being the normal blood sugar, we should not split hairs on slight variations; neither should we expect to maintain the moderately severe diabetic under the most careful dietary management with a blood-sugar level around 100 mg. These patients must be managed so that their strength and nutrition will not be impaired to the extent of incapacitating them for work.

Diabetes is a disease that effects individuals in all walks of life and the prevalence of the disease among the wage-earner makes the economic aspect an important one. It is a chronic disease and we cannot hope to obtain a cure in most cases even with insulin; therefore our management must take into consideration this factor. We cannot hope to hospitalize these cases unless severe and incapable of doing work for long periods of time. Fortunately it is not necessary to hospitalize to any great extent except the severe cases and the cases with complications, as coma. There is a certain disappointment that comes to the patient who has been hospitalized in the initial management. He very often feels that he has had a cure by reason of his stay in a hospital and this has been especially true since the administration of insulin. Unfortunately the idea has been conveyed to the laymen, I think largely through the lay press that insulin represents a cure and this brings disappointment.

Most diabetics can be safely and satisfactorily managed in an ambulatory clinic; they can be safely rendered urine sugar-free; they can be instructed in satisfactory dietary management; they can be furnished insulin and have it administered in the home, once or twice daily, without any risk; they can be instructed to test their own urine daily for sugar and whenever sugar appears to have a half-day of semi-starvation. It is important to have them appreciate the need of frequent checks to know that they are satisfactorily carrying on. The management should be so simplified that the patient can carry on without consuming too much of his time trying to live within his carbohydrate tolerance. If he must weigh every morsel of food and do other needless things, sooner or later he will cease to coöperate, lose interest in his condition and undo all the good that has been done. It has been my experience that most cases of diabetes will coöperate if given the right kind of help.

I know of no disease where individualization in management is so important as in diabetes and in no chronic disease are we so well rewarded for our efforts in management. I do not think it necessary or practical in most cases to hope to maintain a blood-sugar level much below an average of 200 mg. per 100 cc of blood, providing the urine is maintained sugar-free and without acid bodies.

We have managed 43 cases of diabetes, including 3 cases of coma with recovery, in St. Luke's hospital and my private clinic, since November, 1922, to which varying quantities of insulin have been administered. We have not found it necessary or practical to hos-

pitalize all these cases on instituting management and I am convinced that one can safely manage a large per cent of diabetics as ambulatory cases from the start. If one has a satisfactory dietary regimen to place in the hands of the patient and gives the necessary instruction to have him know the simple facts about his disease, he will coöperate just as well and you will save him time as well as money.

Much caution was emphasized about the dangers of the administration of insulin earlier which fortunately has been minimized with experience and now the family doctor as well as the patient safely administers it. In this series of cases we have seen no untoward symptoms arise following the administration except transitory sweating, vertigo, slight vasomotor disturbances, hunger and weakness. These symptoms have not been constant in individual cases and were not in relation to hypoglycemia. Most marked symptoms occurred in hyperglycemia cases where the blood-sugar level was over 200 mg. per 100 cc of blood. The symptoms occur about one hour after administration and no doubt represent the effect of abruptly burning up sugar. The following dietary management, in a general way, has been a routine with individual modifications.

Before instituting insulin treatment the patient was maintained on a liter of whole milk daily given at two- or three-hour intervals until urine is sugar-free. Water is taken very freely. The ordinary case is urine sugar-free in twenty-four hours and the more severe in forty-eight or seventy-two hours. This has furnished a very satisfactory dietary to determine blood-sugar level. When urine is sugar-free, insulin administration is begun in ten-unit doses daily or twice daily, subcutaneously, preferably in loose tissues at angle of arm in order to avoid welt and encourage delay of absorption.

A dietary is pursued, with certain modifications, such as is being used by the Massachusetts General Hospital. The carbohydrate, protein, and fat quantity is determined on the basis of weight, severity, activity of the patient, and insulin administration. The following table brings out detailed facts.

The age of this series of 43 cases varies from ten years to seventy-three years with an average age of fifty years.

The duration of the disease as evidenced by recognition on the part of a physician or history of symptoms varies from one month to twenty-five years, with an average of five and a half years.

Weight: 17 patients remained constant in weight; 17 patients gained in weight; 9 patients lost in weight.

Onset: 12 cases were characterized by abrupt onset; 31 cases were characterized by insidious onset.

Severity: 2 cases were mild; 22 cases were moderately severe; 19 cases were severe; 3 cases of this series of 43 cases were in coma, however all recovered.

Previous management: 5 cases had not been managed previously; 4 cases were managed satisfactorily; 22 cases were managed unsat-

isfactorily; 12 cases showed a fair response to previous management.

Blood-sugar levels before management:

	Case.
150-200 mg. sugar per 100 cc blood	1
200-250 mg. sugar per 100 cc blood	7
250-300 mg. sugar per 100 cc blood	4
300-350 mg. sugar per 100 cc blood	11
350-400 mg. sugar per 100 cc blood	6
400-450 mg. sugar per 100 cc blood	8
450-500 mg. sugar per 100 cc blood	3
600-650 mg. sugar per 100 cc blood	2
750-800 mg. sugar per 100 cc blood	1

Blood-sugar levels after management:

	Case.
50-100 mg. sugar per 100 cc blood	7
100-150 mg. sugar per 100 cc blood	15
150-200 mg. sugar per 100 cc blood	12
200-250 mg. sugar per 100 cc blood	3
250-300 mg. sugar per 100 cc blood	3
300-350 mg. sugar per 100 cc blood	1
350-400 mg. sugar per 100 cc blood	1

Acid bodies in urine before management: 16 cases showed acid bodies in the urine before management; 27 cases were free of acid bodies.

Acid bodies in urine after management: 3 cases showed acid bodies in the urine after management; 40 cases were free of acid bodies.

Urine sugar before management: 41 cases showed an average sugar of 4.2 per cent; 2 cases were sugar-free.

Urine sugar after management: 14 cases were sugar-free continuously; 5 cases had an average sugar from 0.1 per cent (min.) to 3.5 per cent (max.); 24 cases had an average sugar from 0.0 per cent (min.) to 2.2 per cent (max.).

Insulin administration: The quantity of insulin administered to an individual case varied from ten to sixty units. The smallest total quantity given an individual case was 72 units, and the largest total quantity was 1945 units. A number of cases are supplied with 2 cc syringes and insulin with instructions to administer once or twice daily at home. The dosage varies from 1 cc to 2 cc or 10 to 20 units given preferably at breakfast and dinner-time. All cases are checked on blood sugars from time to time.

Caloric intake: The daily caloric intake has varied from 756 calories to 2479.2 calories.

Response to treatment: With one exception all the cases have responded to treatment in a very satisfactory way. The one case of coma responded after being in coma for a period of four days. The response of a profound coma case to insulin administration is the most spectacular demonstration in clinical medicine. The value of

insulin in diabetic coma is superior to most specific sera that we have for any given disease.

Case VI, a moderately severe case did not respond well to the administration of insulin. At first he improved materially, then he lost in weight, his tolerance lessened, his general appearance was not so good, he complained of tire and finally dropped away from the clinic, however he had no other untoward signs.

Case IX, a severe case and who was unsatisfactorily managed in two clinics previously responded to management very satisfactorily. She gained in weight, returned to work but later developed an active pulmonary tuberculosis. It is interesting to note that her weight has been maintained by the administration of 60 units of insulin daily which has allowed a high caloric intake. However her pulmonary condition is unaffected by management.

Case XV was an alcoholic and failed to coöperate on diet, however, his general condition was much improved with insulin administration.

Case XX, a girl, aged ten years, who was a severe case and developed coma was cleared up in twenty-four hours during which time 100 units of insulin were given, afterward developed scarlatina and made a good recovery.

Case XXV, a girl, aged thirteen years, with severe diabetes, abrupt onset, improved materially so that she is urine sugar-free on a practically unrestricted diet.

Case XXVI was managed over a period of years, improved under former dietary management and was restored to work part of the time. His improvement under insulin was remarkable and he has returned to full-time work with weight-gain in spite of a relatively high blood-sugar level.

Conclusions. 1. With our conception of dietary management and the use of insulin, diabetes is no longer a bugbear in practice.

2. While insulin does not give promise of a cure, it improves the mental and physical state of all patients suffering from the disease in a manner that justifies its administration routinely.

3. With a proper conception of dietary management and the proper administration of insulin we can save most cases of diabetic coma and safeguard cases where surgical procedures are necessary.

4. Diabetes being a chronic disease not curable, hospitalization should be reduced to a minimum and emphasis placed on the patient becoming his own doctor.

PERFORATION OF THE ESOPHAGUS DUE TO INSTRUMENTATION (WITH A REPORT OF THREE CASES).¹

BY JULIUS FRIEDENWALD, M.D.,

PROFESSOR OF GASTRO-ENTEROLOGY, UNIVERSITY OF MARYLAND,

AND

THEODORE H. MORRISON, M.D.,

ASSOCIATE IN GASTRO-ENTEROLOGY, UNIVERSITY OF MARYLAND,
BALTIMORE.

(From the Gastro-enterological Clinic of the Department of Medicine of the University of Maryland.)

NUMEROUS cases of perforation of the esophagus, due to the application of the stomach tube, dilator, bougie and esophagoscope in investigating and treating esophageal or gastric lesions, are recorded in the literature. However, the dangers involved in this character of investigation with certain forms of apparatus, especially in some affections of the esophagus, do not appear to have been sufficiently emphasized. It is on this account that the following three cases appear of sufficient interest to warrant publication.

CASE I.—*Cancer of the Esophagus with Perforation into the Left Pleural Cavity and Death from Pyopneumothorax.* Mrs. J. H., married, aged thirty-one years, presented the following history: Her family and personal history were negative. She had always enjoyed good health until three months previous to admission, when difficulty in deglutition was first noted. At first this was only observed with solid food, and finally, after two months, there was absolute inability to swallow solids, while even liquids were now passed into the stomach with difficulty. Recently the act of deglutition was accompanied with great pain; frequent regurgitation of mucus occurred, but never of blood. There were constant eructations and obstinate constipation. On examination the patient was found to be well nourished; the glands are nowhere enlarged; the mucous membranes are red; the heart, lungs and abdomen are normal. The blood examination shows 5,000,000 red corpuscles and 10,000 white cells, with the urine normal. In introducing the soft tube, a resistance was felt, through which the tube could not be passed. When measured this was found to be 36 cm. from the teeth. Attempts were made to introduce various sizes of soft-rubber tubes which, however, could not be passed through the stricture. The hard tubes were then introduced. The large-sized bougies could not be passed into the stomach,

¹ Read at the annual meeting of the American Gastro-enterological Association, April 30, 1923.

but those of small size were passed without difficulty. The obstruction was constantly located at from 36 to 38 cm. from the teeth. The second deglutition murmur was delayed often to forty seconds, and at times it was entirely absent.

The patient was frequently seen, and constantly complained of pain in swallowing and of great difficulty at times of getting even the smallest quantity of milk into the stomach. It became difficult finally even to pass the small-sized bougies.

Inasmuch as the patient was now able to swallow only extremely small amounts of liquid nourishment, gastrostomy was decided on. At the time of operation even a small-sized bougie could not be passed while the patient was under anesthesia. A gastrostomy was performed and a small olive sound passed from below upward, when an obstruction was noted about 10 cm. above the cardiac orifice of the stomach. The bougie was passed through the stricture area; a string was attached to it and withdrawn, and larger sounds were then drawn through from below, attached to the cord, until the largest passed with ease. In passing the first or second sound something was felt to give away. The stomach was sutured to the abdominal wall and closed.

The patient did well for four days. Her temperature had remained between 99° and 100°F. and her pulse 100 to 108, and she was able to retain small amounts of egg albumen, milk and broth. On the fifth day she complained of intense pain in her left chest. There was a marked dyspnea and the temperature rose to 103°F., and the pulse to 140. A pyopneumothorax was discovered in the left chest and a quart of brownish pus aspirated.

On the following morning a rib at the angle of the scapula was resected, when a large quantity of foul-smelling pus was evacuated. The patient did not rally from the operation; her temperature rose to 104° F. and her pulse to 160; she died on the following morning.

At autopsy a perforation was noted in the cancerous mass in the esophagus. This mass was ulcerated, the largest diameter being 1.5 cm. in length. The circumference of the ulcer was very hard and indurated; the base soft and dipping deeply into the mucosa; along the inferior surface of the ulcer the opening was found, indicating the point of perforation. In placing the esophagus in its normal position an almost complete obstruction was presented at the point of stricture. Microscopically, the mass was found to be an adenocarcinoma.

The case is interesting as showing one of the rather rare results of rupture produced by instrumentation in a carcinomatous growth of the esophagus.

CASE II.—Carcinoma of the Esophagus with Perforation into the Right Lung and the Production of Pneumonia and Abscess; Spontaneous Cure of the Lung Abscess with Fatal Termination from the

Cancer. J. S., female, aged sixty-nine years, consulted us on September 1, 1920, complaining of difficulty in swallowing. The family history is unimportant. The past history is also negative, the patient never having been ill before the onset of the present affection, excepting for the suggestion of some apparent gall-bladder attacks several years previously. She has always enjoyed a good digestion, the bowels moving regularly once daily, and the appetite has always been normal. The patient dates the onset of her present illness to six years back, when she had several attacks of abdominal discomfort with pressure around the heart and dyspnea. These required hypodermics of morphine for relief. She continued on fairly well for several years, except for the appearance at infrequent intervals of similar attacks, which were milder in character and readily relieved by the administration of soda and hot water. Three months before the patient consulted us she began to experience, on the swallowing of solid food, a sensation of weight and pressure in her chest. The dysphagia was soon followed by regurgitation and gradually solids were excluded from the dietary; but soon liquids, too, began to create the same difficulty. These symptoms grew progressively worse; anorexia appeared, very little food was ingested and marked loss of weight ensued.

The physical examination made at this time revealed practically normal findings. The abdomen appeared normal; no enlargements or tender areas were noted. On attempting to pass a stomach tube, however, a definite resistance was encountered at about 7 inches from the incisor teeth, and on extracting the tube some blood was observed on the tip end. A roentgenographical examination revealed the following findings: A definite obstruction of esophagus at the level of the fourth rib; no irregularity at the cardiac end; heart and lungs negative; stomach on level of crest, being pulled definitely to the right upper quadrant; peristalsis hyperactive; irregularity in the pyloric region; no eighteen-hour retention; duodenal cap outline indefinite; cecal retention; hepatic flexure 4.5 cm. above the crest; colon position good.

The blood examination, including the Wassermann test, was negative. A blood-sugar tolerance test revealed a high sustained curve which is commonly noted in malignant affections of the gastro-intestinal tract. In this particular case this finding is of negligible diagnostic value, since sugar was repeatedly observed in the urine of this patient later in the course of her illness, indicating that she may have been a potential diabetic with a diminished carbohydrate tolerance even at the time when the test was made.

In view of the history and findings a diagnosis of carcinoma of the esophagus near the cardia was made; the patient was referred for radium therapy, in anticipation of which the growth was inspected by direct esophagoscopy. Subsequently, several radium applications were made with apparent clinical improvement.

Following the last examination with the esophagoscope, the patient complained of severe pain in the lower substernal region with marked dyspnea and cough. The next evening she had a temperature of 101° F., with cough and pain in the right chest. On the third day, on account of the discomfort, cough and general distress, the patient was sent to the Hebrew Hospital (October 2, 1920).

The following report of the physical examination was made at the hospital the next morning: Temperature, 101° F.; pulse, 102; respiration, 28; blood-pressure, 118/54.

General appearance: The patient is an elderly white woman, fairly well nourished, lying in bed propped up on a back-rest, and at short intervals is seized with paroxysms of coughing, which last several minutes, causing dyspnea and cyanosis. The pulse is synchronous, of fair volume and tone, somewhat irregular, an extrasystole being interposed at about every sixth beat. The heart is somewhat enlarged, the apex-beat being palpable in the fifth interspace, 8 cm. from the midsternal line. The right cardiac dulness is 5 cm. to the right and 10 cm. to the left of the midsternal line in the fourth interspace. The heart sounds are clear, but there is some arrhythmia, an extrasystole being present about every sixth beat. There is a slight suggestion of a systolic murmur at the apex, which is not transmitted to the axilla. The lungs do not show any lagging on deep inspiration, the expansion being apparently equal on both sides. There is some impairment of the percussion note over the right chest to the third rib, with definite dulness to the base in the back. The breath sounds are short and jerky, with prolonged expiration over the entire right chest, but most marked from the third rib down. Exaggerated vesicular breathing was heard over the left apex. Numerous moist crepitant rales were noted over the right chest, which persisted after coughing, and some scattered moist sounds were detected over the left base. Later on whispered pectoriloquy and cavernous breathing were observed in the right base posteriorly.

Laboratory findings: The urine repeatedly showed sugar and traces of albumin, the specific gravity ranging between 1.025 to 1.034. The blood picture was as follows on October 3, 1920: White blood cells per 1 cm., 13,700; red blood cells per 1 cm., 3,936,000; hemoglobin (Sahli), 66 per cent; color index, 0.84. Differential count: Small lymphocytes, 17.5; large lymphocytes, 3; large mononuclears, 2; transitionals, 5.5; polymorphonuclear neutrophils, 72; eosinophils, 0; basophils, 0. Blood sugar on fasting stomach, 0.25; blood urea N, 16 mg. Stool: Offensive yellowish fluid; stool containing no occult blood, eggs or parasites. Sputum after a few days became purulent, foul smelling, containing no tubercle bacilli nor elastic tissue, but numerous Gram-positive diplococci. Roentgen-ray studies (October 4, 1920): Roentgen-

ray examination revealed a large area of consolidation at the right base, with cavity formation.

October 11, 1920: On swallowing an opaque meal, an obstruction at a point opposite the sixth thoracic vertebræ was noted fluoroscopically where the lumen of the esophagus became definitely narrowed and irregular. The obstruction was not complete, however, as the meal eventually trickled into the stomach. The diagnosis arrived at was cancer of the esophagus, associated with consolidation of the base of the right lung and cavitation. This examination was repeated several times, when occasionally bismuth was noted trickling into the right lung from the esophagus at the point of stricture.

The course of this case in the hospital was interesting: There was a gradual elevation of the temperature, reaching 103°F. on the third evening. This peak was maintained for three evenings with a drop of a degree or more in the early morning. There was a gradual decline for two weeks, though the septic character continued along. During the early part of this period the patient was affected with severe paroxysms of coughing, which were usually followed by the expectoration of large quantities of yellowish, purulent, foul-smelling material. Deglutition became more and more difficult, being accompanied by paroxysms of coughing. The lungs gradually cleared up, the abscess cavity entirely disappeared and the expectoration practically ceased. On account of the increasing weakness and dysphagia gastrostomy was advised. The operation was performed under local anesthesia on November 15, 1920. The patient's general condition improved somewhat, and on November 27, 1920, she left the hospital. Several weeks later, when seen, she appeared still in a good condition. The lungs were entirely clear; she was swallowing small amounts of liquids, although most of her nourishment was administered through the gastrostomy opening. Soon afterward her condition changed for the worse, and about six weeks after leaving the hospital she died. An autopsy was not permitted.

CASE III.—*Carcinoma of the Esophagus with Perforation into the Right Lower Bronchus and Bronchopneumonia followed by Death.* Mr. R. M., married, aged forty-nine years, consulted us on August 12, 1922, complaining of dysphagia. He had always enjoyed good health and had never required any medical attention. His family history is unimportant. His digestion had always been normal. The difficulty in swallowing gradually increased, and in about a month after the onset the patient was forced to limit himself to milk, raw eggs and water. There was a sensation of weight and pressure in the chest following deglutition. After a thorough examination, which included a roentgen-ray and esophagoscopical investigation, a diagnosis of carcinoma of the esophagus near the

cardia was made and the patient referred to the Kelly Sanitarium for radium therapy. The Wassermann reaction was negative. Two radiations were given with some improvement after the first treatment, but none following the second. An attempt was made to increase the lumen of the esophagus and to relieve the patient by means of an electrically heated bougie, according to the method advocated by Dean. Immediately after this procedure the patient complained of pain and a sensation of heat in his chest. Three days later he noted that the taking of food or water caused violent paroxysms of coughing. He was sent to the Union Memorial Hospital for observation and treatment on January 28, 1923. The physical examination at this time revealed a well-developed, undernourished individual, somewhat dyspneic and restless. The thorax showed an increased antero-posterior diameter and a costal angle somewhat greater than 90 degrees. The vocal fremitus was normally transmitted throughout both lungs. The percussion note was slightly hyperresonant and the breath sounds broncho-vesicular. The expiration was prolonged and there was an expiratory wheeze, especially marked over the right base. There were no rales. The heart was normal; the sounds distant but clear. Since the patient refused any further palliative measures, a consultation was held to determine the advisability of radical surgery. Before deciding this question the following fluoroscopical report was obtained: Watery mixture of barium passes freely down the esophagus to the level of the third interspace in front, where it meets an obstruction which is apparently complete. Then the barium apparently disseminates throughout the walls of the esophagus. This was watched several times and constantly it was observed that a little barium passed into the right lower bronchi. After due consideration it was decided that an operation would be utterly futile. The patient was no longer able to take any nourishment by mouth, and nutrient enemata were administered at regular intervals. He was sent home, where he was kept as comfortable as possible by hypodermic administrations of morphine. The cough was very harassing and the sputum had a fetid odor. Toward the end signs of bronchopneumonia appeared, with temperature and bloody sputum, and on February 13, 1923, the patient died.

Discussion. According to Ballin and Saltzstein, perforation of the esophagus has been reported as due to the following lesions:

- A. Congenital malformations.
- B. Neoplasms.
- C. Aneurysms.
- D. Trauma.
 - 1. Esophageal instrumentation.
 - 2. Surgical wounds.
 - 3. Stab and gunshot wounds.
 - 4. Foreign bodies.

E. Spontaneous rupture.

F. Inflammation.

1. Acute esophagitis.
2. Diverticulæ.
3. Simple or peptic ulcer.
4. Luetic ulcer.
5. Tuberculosis.

We desire in this report to limit ourselves to a brief discussion of those cases which are directly the result of instrumentation. When one considers the anatomy of the esophagus, the thin and delicate walls, the normal constrictions occurring at the entrance of the gullet, the point of crossing of the aorta, the crossing of the left bronchus and the cardia and its course, which is not that of a straight tube but following the direction of the cervical and dorsal segments of the spinal cord, it is not surprising that many cases of perforation have been noted. This is more readily conceivable when we realize that esophageal instrumentation is usually practised on patients who have swallowed some foreign substance or in whom diseased esophageal walls exist, on account of which symptoms referable to the gullet have occurred. This accident occurs more readily where the esophagus is the seat of some congenital anomaly or in the presence of an unsuspected aneurysm or diverticulum. Again, on account of the frequent stomach and duodenal instrumentation necessary, when investigating and treating patients presenting gastro-intestinal symptoms, the esophagus is rendered liable to injury and possibly to perforation. This complication is more likely to follow the use of hard instruments, such as the various bougies and the esophagoscope, rather than soft tubes.

In order to diminish the occurrence of this serious injury, certain contraindications to instrumentation must be borne in mind. Of these the most important are: (1) Water hunger and cachexia, on account of which it is best to postpone the examination until the vitality of the patient has been partly restored by means of nutrient enemata or through gastrostomy feedings; (2) severe prostration due to any cause, such as high temperature, cardiac decompensation, advanced tuberculosis, shock, etc.; (3) acute inflammatory conditions following the ingestion of caustic poisons; (4) recent hemorrhages.

Numerous cases of perforation have occurred following the careless and injudicious application of instruments. In quite a few instances rupture of the esophagus has been occasioned by means of dilatation for stricture in the hands of specialists, indicating that even with the best technic accidents may occur. A careful history, together with a thorough physical and roentgen-ray survey, should precede every instrumental examination. In the presence of esophageal diverticulæ, or where multiple strictures

exist in the same patient, a string should first be swallowed and used as a guide before bougies are passed. Esophagoscopy in such cases should be practised with particular care, and the progress of the esophagoscope should be directed slowly with gentle pressure while keeping the lumen of the gullet under the direct vision of the operator.

According to Ballin and Saltzstein, perforation may occur into the neck, great vessels, respiratory tube or into the thorax. As a consequence fistulæ may develop. If this occurs in the cervical region an esophago-cutaneous fistula results; if perforation takes place in the respiratory tract there will ensue either an esophago-tracheal, esophago-bronchial or esophago-pulmonary fistula. When it occurs directly into the pleural cavity a pyopneumothorax develops. Should the break be through the thoracic wall there will be formed a transpleural esophageal fistula, *i. e.*, a communication between the esophagus and skin by way of the pleural cavity. When perforation occurs into an aneurysm or a bloodvessel hemorrhage and death will follow immediately. In a recent publication H. M. Scoville reports a case of a white boy, aged nine years, who was fed through a nasal tube on account of unconsciousness and spasticity of his jaw muscles due to encephalitis. The tube was left *in situ* and nourishment administered regularly for about a week, when the patient suddenly developed a hemorrhage and died. At autopsy a perforation of the esophagus into an anomalous right subclavian artery was demonstrated, which was due to the traumatic erosion of the bloodvessel by the tube. Mediastinitis, pneumonia, bronchiectasis, abscess formation, peritonitis and rupture, followed by death, are some of the other complications which at times follow perforation of the esophagus.

The symptoms of perforation of the esophagus depend largely on the location of the rupture. In all instances when this condition occurs following the use of instruments, there is a sudden, severe pain referable to the region of the esophagus. If this takes place into an aneurysm hemorrhage occurs, together with the accompanying signs of shock, and usually a quick, fatal termination is included in the sequence of events. Sudden perforation into the respiratory tract is usually fatal. In those instances where the patient survives the immediate effects of the accident pneumonia, pulmonary abscesses, bronchiectasis and fistulæ may develop. Coughing and choking spells when the patient attempts to eat indicate esophago-bronchial communication. At times food particles may be expelled in the drainage from the transpleural fistulæ. When an ulcer located in the lower end of the esophagus is perforated by an instrument the signs are similar to those of a perforated gastric ulcer, that is, abdominal rigidity, respiratory distress and indications of peritonitis.

The diagnosis of instrumental esophageal perforation is usually

easily made. In our first case the operator, by his tactile sense, could feel that something had given away as he manipulated the bougie. In the second case the sudden pain in the esophageal region, followed by the development of a traumatic pneumonia and the expectoration of pus, rendered the diagnosis comparatively simple. In some instances a roentgenogram may show the barium mixture escaping from the esophagus into the thorax, which was observed in our second and third cases. Vomiting of pus and the rapid development of a pyopneumothorax are suggestive signs of perforation of the esophagus. As has already been noted, coughing and choking spells following the ingestion of food indicate respiratory involvement. In many cases food particles have appeared in the fistulous opening in the skin.

The prognosis in these conditions is usually very grave. When perforation occurs into an aneurysm or the respiratory tract the accident is usually fatal. In some instances of respiratory-tract involvement the patient may survive if the resulting complication is arrested. A pyopneumothorax may be treated by thoracotomy, and drainage and a cure effected provided the esophagus is not the seat of malignant disease. Ballin and Saltzstein report a case of spontaneous cure in a patient with pyopneumothorax, following a lobar pneumonia in which perforation occurred into the esophagus, with the formation of an esophageal fistula. Thoracotomy was performed, and subsequently ingested food particles were demonstrated in the pus discharge. The drainage tube was kept in place for a period of a year, and during the difficult first few weeks the patient was fed through a duodenal tube left *in situ*; then the fistula became sufficiently narrowed to allow most of the food to pass into the stomach. Finally, it closed entirely and perfect recovery resulted. Although this is not an instance of esophageal perforation of the type that we are having under discussion, it is quite conceivable that a similar pathological process might occur as a consequence of instrumentation.

Conclusions. We wish again to call attention to the fact that instrumental esophageal perforation is not an uncommon accident. In order to diminish the frequency of this serious complication, a careful physical history and roentgen-ray survey should precede the instrumental investigation. In the presence of diverticulæ or multiple strictures a string should be utilized as a guide in passing esophageal instruments. Finally, in utilizing the esophagoscope in such cases, the progress of the instrument should be directed with gentle pressure and the lumen of the esophagus kept under the direct vision of the operator.

A DISCUSSION OF THE ETIOLOGY OF ASTHMA IN ITS RELATIONSHIP TO THE VARIOUS SYSTEMS COMPOSING THE PULMONARY NEUROCELLULAR MECHANISM WITH THE PHYSIOLOGICAL BASIS FOR THE EMPLOYMENT OF CALCIUM IN ITS TREATMENT.

BY F. M. POTTENGER, M.D.,
MONROVIA, CALIF.

Introduction. Asthma has long been looked upon as a disease without an anatomical basis, due largely to the fact that it was considered to be a neurosis, and, as such, to have no pathological-anatomical changes. Recently, however, the subject has been studied anew, and after a most painstaking investigation it has been shown that asthma has apparently, as an essential pathology, a thickening of the entire bronchial wall, which at times almost obliterates the lumen of the tubes.¹ The thickened musculature and enlarged mucous glands most probably afford an instance in which anatomical changes result from an overstimulation of a physiological process, for in asthma the vagus nerve, which stimulates both the musculature and the secretory glands of the bronchi, is in a state of hyperirritability; consequently these tissues are subject to prolonged vagus action.

Studies of asthma have led investigators to approach the subject from many different angles. Early opinion considered it a pure neurosis. Some have attributed it to errors in diet without regard to any definite opinion as to the nature of such errors. This idea is much older than our present knowledge of food sensitization. Others have attributed it to reflex causes, the reflex arising in the nose, sinuses, gastro-intestinal canal, urogenital system, or, in fact, in any organ or tissue of the body whose afferent nerves are able to mediate with the pulmonary branches of the vagus. Brown² considers it due to an inability on the part of the patient to expire in the normal easy manner, caused by "respiratory-tract catarrh," and calls his theory the "non-passive expiration theory." The most recent suggestion, and the one which is claiming most attention today, is that of anaphylaxis. Those interested in this particular phase of the subject have found substances almost without number, to which asthmatics may become sensitized, such as pollen, horse dandruff, feathers, hair, bacteria and foods. Babcock,³ Walker,⁴ Rackemann⁶ and Cooke⁸ are among the early and ardent students of this phase of the subject. The idea of sensitization is a great advance in our etiological conception, but it must not be interpreted too narrowly. With present knowledge it surely cannot be considered as the only factor active in the production of paroxysms. Some writers are too prone to hold to

one cause and exclude all others. Asthma is not so simple as that. It must be approached from a very broad viewpoint. The underlying reacting capacity of the individual's bronchial neuromuscular mechanism must be taken into consideration as well as the exciting cause.

Cooke and Vander Veer⁹ analyzed inheritance as a factor in sensitization in 504 patients in whom the family history was complete, and found that sensitization was present in one or both parents in 244 instances, making 48.4 per cent. In 76 normal persons sensitization was present in only 14.5 per cent. Comparison of these figures shows a very strong hereditary tendency to sensitization. Wolff-Eisner¹⁰ suggested that hay-fever, which is a close ally to asthma, is due to the pollen protein acting upon a hypersensitive individual. Blackfan¹¹ states that the condition of hypersensitiveness may be present at birth and that those with this type of heredity are prone to asthma, eczema, urticaria and hay-fever. Scheppegegrell¹² states that of 1000 cases of hay-fever analyzed 43 per cent also suffered from asthma, and comments further that the actual percentage is probably much higher because many minor paroxysms are not diagnosed. Pinness¹³ states that 27 per cent of his patients gave a history of positive heredity. Godall,¹⁴ in analyzing 3502 consecutive cases of serum sickness, found a great number who responded quickly with all the symptoms of profound anaphylactic shock—just as though they had been sensitized by previous injections, although they had not been given horse serum before. A considerable number of these were asthmatics. He considers that they were born anaphylactic. In this connection, Wells¹⁵ says that fatal anaphylaxis is practically limited to asthmatics. When all the facts are carefully weighed the argument seems strongly supported that there is something in the make-up of the asthmatic patient which makes him susceptible to the action of proteins, reflex stimulation, climatic change and physical and chemical irritants.

No study of asthma can be considered complete unless it takes into account those factors which are accountable for the paroxysms, as well as the exciting agents. The following subjects require careful consideration:

1. The susceptibility of the patient to react to causative agents:
 - (a) Hyperirritability of the bronchial division of the vagus nerve, usually a general vagotonia as well;
 - (b) relative increase in potassium as compared with calcium ions in the cells of the bronchi;
 - (c) changes in those incretions which disturb the balance in either the nerve mechanism or the ion content of the cell and probably the colloidal phases of the cell itself, particularly the thyroid, the pituitary and parathyroids.

2. Substances to which the patient becomes sensitized—pollen, animal emanations, foods, etc.

3. Inflammation and other irritations which cause reflexes to express themselves in the pulmonary branches of the vagus, such as those arising in the nose, sinuses, gastro-intestinal tract, genital system and even the lung itself.

4. Such stimulating factors as are associated with climatic change—physical and chemical irritants.

The Relationship of Asthma to the Visceral Nerves. I became convinced several years ago that we could probably make headway in our understanding of visceral diseases by classifying the various syndromes, which present during their course, according to the manner in which they affect the two components of the vegetative nervous system.¹⁶ The symptoms accompanying these diseases may be arranged into sympathetic and parasympathetic syndromes, according to whether the irritability of the one or the other system is in the ascendency, thus: The lack of appetite, deficient secretion in the gastro-intestinal tract and relaxed musculature, resulting in constipation during acute toxic states, constitutes a sympathetic syndrome; the rapid heart and altered blood-pressure, another; hyperchlorhydria, with increased muscle tonus in the gastro-intestinal canal, colicky pains and spastic constipation, a parasympathetic syndrome; the nasal irritation, with increased nasal and lacrimal secretion in hay-fever, another; likewise the spasm of the bronchial musculature and the increased secretion which is evident during paroxysms of asthma. The rapidity of heart action and increased respiratory effort during asthma result from the deficient oxidation, and may be looked upon as incidental symptoms and not as an integral part of the asthmatic syndrome. The same is true of emphysema. In previous discussions of asthma I called attention to the relationship which the symptoms bear to the vegetative nerves,^{17 18} but did not appreciate the part which the cells themselves take in the reaction. I endeavored, however, to emphasize the fact that a broad point of view is necessary to its understanding, as is evident from the following quotation.¹⁸

“Asthma is a disturbance in function. It is an increase in tonus of that portion of the parasympathetics which supplies the bronchial musculature and mucous membrane. Its causes may be as diverse as the irritants which may be applied to the nerve centers which give origin to the pulmonary fibers, or to the peripheral nerves that are in reflex relationship with them.”

In the bronchi the vagus of the parasympathetic system and the sympathetics are antagonistic in action. Stimulation of the vagus causes contraction (spasm) of the bronchial musculature and an increase in bronchial secretion, while stimulation of the sympathetics relaxes the bronchial musculature and decreases the bronchial secretion.

This antagonistic relationship of these two components of the

vegetative system is definite, as may be inferred from the fact that the commonly successful method of relieving the paroxysms of asthma consists either in using remedies which will inhibit the action of the vagus or those which will cause a relative increase in the antagonistic sympathetic action. Atropine is a drug with the former action, but it cannot be given in full inhibiting doses without causing great discomfort to the patient, so it is of limited value. Adrenin has been the most successful individual remedy heretofore used against the paroxysm. Adrenin effects this result by producing the same action upon the bronchial musculature as though the sympathetic nerves were stimulated, and so tends to restore the normal sympathetic-parasympathetic balance. Its usefulness is greatly limited by the fact that its action is transitory. It will relax the spasm and give relief within a few minutes after it is injected, but its effect usually lasts only a few hours when it must be repeated. The effect of sympathetic action in relieving asthmatic paroxysms has been noted by the writer in the acute toxemias accompanying tonsillitis, influenza, pneumonia, typhoid and an exacerbation in tuberculosis. In each instance asthmatic paroxysms were in abeyance during the toxic stage of the intercurrent affection. The effect in these instances was due to the toxins stimulating the sympathetic mechanism sufficiently to inhibit the vagus and relax the spasm. This action may affect both the nerves and the ions in the peripheral tissue cells.

Relationship of Ion Content of Cells to Vegetative Nerves. In studying the cause of symptoms I have been gradually led to see that action in the neuromuscular apparatus depends to a great extent upon the condition of the body cells. The condition of the cell determines to a very remarkable extent its own action, and likewise the manner in which it will react to nerve and chemical stimuli. Under differing circumstances the cell may differ physically, that is, in the physical character of the colloids which compose it, or in its content in electrolytes, and each change alters its reactivity.¹⁹ Among other electrolytes the body cells contain calcium, potassium and sodium in certain relative proportions. A variation in the relative amount of these various ions held by the cell alters its function in the same manner as though its nerve equilibrium were disturbed; in fact, the ion content is an essential part of the neuromuscular mechanism.

One fact which emphasizes the intimate relationship between nerve and ion content of the cell is that these electrolytes can be divided into sympathetic and parasympathetic groups in a manner similar to adrenin, ergotoxin, nicotine, atropine, pilocarpine and acetocholin. Sydney Ringer,^{20 21 22} in 1881-1882-1883, made observations bearing upon this subject long before sympathetic and parasympathetic action was understood. Ringer, in perfecting the solution which bears his name, demonstrated the antago-

nism between the calcium and potassium ions in the cell, and pointed the way, which has been all too tardily followed, for understanding the nature of cellular action. Sodium chloride solution had proved satisfactory for the histological examination of fresh tissues and for the dilution of blood, but it failed to furnish a satisfactory medium for the study of muscular action when the organ (heart) was removed from the body circulation. Ringer found that contraction of the heart of the frog could not be carried on after removal from the body for any length of time when a saline solution, isotonic with the blood, was used for perfusion. In experimenting with different substances he added calcium and found that the heart, after it had ceased beating in saline solution, could be made to contract again, but that diastole was prolonged and imperfect. By the addition of potassium to the solution already containing calcium, he strengthened the diastole and the heart-beat forcibly in both systole and diastole. He then added sodium bicarbonate and noted that the completeness of the contraction still improved. He considered that the value of the sodium was due to its rendering the solution alkaline like the blood. Recent experiments as well as clinical application, however, show that aside from its effect as an alkalizer, sodium produces an action similar to potassium—at least in the intestines.

Now that we better understand vegetative neurology, we can readily see that calcium in Ringer's experiments acts in harmony with sympathetic stimulation, and potassium—and to a less extent sodium—in harmony with parasympathetic (vagus) stimulation. Later Howell²³ found that the inhibitory action of the vagus upon the heart was absent without the presence of potassium in the Ringer's solution, and Howell and Duke²⁴ found an increase in the potassium content of Ringer-Locke's solution which had passed repeatedly through the heart of a mammal under vagus stimulation, from which experiments Howell called attention (1906) to the fact that vagus action was in some way connected with the setting-free of potassium ions.

Supplementary to the work of Howell, Zondek's²⁵ recent experiments are of great interest. He found that in stimulating the vagus supplying an experimental heart, and, carrying the perfusate through a second heart, he could produce the same effect in the second heart as though its own vagus were stimulated. On the other hand, stimulating the sympathetic nerves and carrying the perfusate through a second heart produced the same effect in the second heart, as though its own sympathetics were stimulated. Such experiments as those of Howell and Zondek, as well as those of many others, indicate definitely that stimulation of sympathetics and parasympathetics produces different effects upon the cells of an organ, and that they cause these cells to give out into the blood stream certain definite substances which differ according to which

system of nerves is stimulated. Clinical experience also bears this out in other tissues.

With our newer conception of physiology, biochemistry and biophysics, we must assume that nerve stimulation results in changing the cell so as to cause it to take from or give out certain substances into the blood stream. It is quite probable that this effect is partly caused by producing changes in the colloids of the cells. There is no doubt that action in body cells is associated with changes in permeability of the cell membrane and the binding more firmly or giving off of various ions.

Among other workers who have reported important studies bearing on this interesting phase of medicine may be mentioned Kraus and Zondek,²⁶ Abderhalden,²⁷ Kolm and Pick,²⁸ Andrus and Carter,²⁹ Daly and Clark,³⁰ Hammett,³¹ Loewi³² and Sollmann.³³ The work of these observers has established beyond doubt the interdependence of the sympathetic nerves and calcium ions in the cell on the one hand, and the parasympathetic nerves and potassium ions on the other. This is a very important contribution to the understanding of the action of the neurocellular mechanism and offers important suggestions for a better understanding of the manner in which diseases produce their effects upon the organism, and further provides certain definite principles which may be made the basis of rational therapeutic endeavor.

Altered Nerve and Cell Reactivity of the Individual Included in Etiology of Asthma. It would really seem that asthmatics belong to a particular group of individuals who possess a vegetative nervous system in which parasympathetic activity prevails. In order for such nerve status to exist there must be certain conditions in the body cells themselves. Increased parasympathetic action (vagus in asthma) presupposes a relative increase in potassium as compared with calcium ions in the cells, either an actual decrease in the calcium or an actual increase in the potassium. It is quite probable that this state of relatively increased parasympathetic-potassium activity in the cells may be partly inherited and partly acquired.

It is of interest in the discussion to understand where the reaction takes place in asthma. There is a close relationship in the reaction in asthma to that of anaphylaxis. In fact, in those cases due to protein, sensitization seems identical. The weight of evidence seems to favor the view that the principal seat of activity in anaphylaxis is in the cells themselves.^{15 34} Besredka³⁵ was early inclined to think that the seat of the reaction was in the central nervous system, but later accepted the theory that it is in the body cells themselves. Zinsser³⁶ sums up this phase of the subject in the following manner:

"Limiting ourselves for the present to the phenomena of anaphylaxis in which non-cellular antigens are employed, we may safely say that the evidence furnished by the incubation time

necessary in passive anaphylaxis by the transfusion experiments of Pearce and Eisenbrey³⁷ and of Coca,³⁸ and most conclusively by the work on isolated tissue of Schultz,³⁹ of Dale⁴⁰ and of Weil,⁴¹ shows conclusively that the hypersusceptible state is largely determined by a changed reaction capacity to the specific antigen on the part of the fixed tissue cells—an "allergie" which is probably due to the presence of specific antibodies in the substance of the cell protoplasm, and incidentally accounts for such effects as the skin reactions."

Hypersensitive cells during the reactive stage show change in their colloidal phases, which can be removed by desensitization. That this change in colloidal arrangement of the cells is responsible for a shifting of the ion equilibrium may be conjectured. That it is evidenced by a lessened sympathetic action, which is associated with a relative deficit in calcium ions, an increased permeability of the cell membrane and an associated hyperactivity on the part of the parasympathetic nerves is definite.

Many asthmatics suffer from other manifestations of protein hypersensitization, such as hay-fever, urticaria and eczema, and show other manifestations of hyperactivity on the part of the parasympathetic system (vagotonia), such as increased oculo-cardiac reflex, bradycardia, hyperchlorhydria and spastic constipation; furthermore, since many of them give a history of similar conditions in parents and grandparents and other members of the family, it is of great importance to ascertain if there is not some defect in their neurocellular mechanism—either a decrease in sympathetic irritability or a decrease in the calcium ions in the cell on the one hand, or a hyperirritability on the part of the parasympathetics or an increase in the potassium ions in the cell on the other hand—which antedates and is responsible for their becoming asthmatic. It is easy to understand how such individuals could manifest this imbalance, now in one tissue and now in another, causing hay-fever, asthma, bradycardia, hypermotility and hypersecretion in the gastro-intestinal canal, or manifestations in the skin, such as urticaria and eczema, according to the tissue involved. It is also easy to understand how those individuals who manifest this hyperirritability on the part of the neurocellular mechanism of the bronchi would respond with an asthma whenever this system was stimulated unduly, either reflexly or by such a condition as protein sensitization, or by changes in weather and climate or mechanical and chemical irritants. In the causation of this underlying condition, we must bear in mind that there are certain glands of internal secretion which bear an important relationship to calcium metabolism and the activity of the sympathetic and parasympathetic systems. Their possible part in furnishing a basis for the underlying relative hypersensitiveness of the parasympathetic-potassium mechanism must be carefully investigated.

Asthma can readily be classified on the basis of these studies as a condition in which the bronchial neurocellular mechanism reacts profoundly to stimuli which do not affect normal individuals, according to Eppinger and Hess,⁴² a local vagotonia. But vagotonia, which has heretofore been considered to be a condition of hypersensitiveness of the parasympathetic nerves, of which the vagus is the largest and most widely distributed, must be given a broader definition. It becomes a condition not of the nerves alone, but of the cells acted upon as well; a condition in which the ion content of the cell is disturbed and the permeability of the cell membrane increased and in which the most evident change, according to existent knowledge, consists in a relative overbalancing of the potassium-calcium equilibrium in favor of potassium, so that a reaction on the part of the cells, at least when stimulated by the parasympathetic nerves, results in action which is beyond the bounds of physiological reaction. With present knowledge we can fix the reaction, which is recognized as the paroxysm in asthma, definitely upon the neurocellular mechanism which is associated with the vagus of the parasympathetic nervous system. We must recognize, however, that the reaction probably may be precipitated in two ways: (1) By direct action upon the cells; (2) by stimulation of the bronchial fibers of the vagus nerve.

Administration of Calcium Ions for the Relief of Asthmatic Paroxysms. In applying this knowledge of the action of the neuromuscular mechanism to asthma, the possibility of relaxing the bronchial spasm and relieving the bronchial secretion by changing the electrolytic content of the cells seemed feasible. Inasmuch as an increase in the relative amount of calcium in the cell causes the same physiological action as stimulation of the sympathetic nerves, I decided that there was important therapeutic possibilities in introducing sufficient calcium to restore the normal neurocellular equilibrium of the bronchial tissues. Not having at hand any definite way of determining how much would be required, it was decided to begin the treatment with small amounts (5 cc of a 5 per cent solution intravenously, increasing to 10 cc if necessary) and to repeat every few days, watching the effect carefully. The patients under trial were kept in bed continuously.

The calcium chloride used was in sterile ampoules containing 5 cc of a 5 per cent solution. The contents of each ampoule is equivalent to 0.25 gm. of the salt. It has been found best to inject the solution slowly, taking from four to five minutes for the 10 cc, in order to avoid mild untoward effects. At the above rate of injection a slight facial flush is noted and the patient is conscious of a feeling of warmth more pronounced in the face and in or over the abdomen. The blood-pressure rises from 5 to 10 points following an injection, but usually returns to normal within thirty minutes. The pulse-rate in asthmatics may drop 10

to 20 points per minute and persist at the lower rate for a short period.

When injected more rapidly the patient complains of a feeling of intense heat in the skin and breaks out in a profuse perspiration. There is a feeling of constriction in the throat and a feeling of nausea, persisting for upward of thirty minutes. There is also a burning sensation in the rectum. Dilatation of the pupil is questionable. One patient developed an aphonia, lasting for a few minutes.

Calcium has long been recommended by the mouth in the treatment of asthma, but apparently without any particular understanding of how it acts or what doses are necessary to produce an effect. Nor has it, as far as I am able to find, received any particular support. In looking through successive numbers of a popular year-book from 1903 to 1922 I find no reference to it; neither did I in several works on practice of medicine. It is recommended, however, in circulars sent out by commercial houses who specialize in putting up drugs for intravenous medication. I also find it recommended by Meyer and Gottlieb⁴³ in their work on pharmacology, but for oral administration. A recent report of its intravenous administration in the treatment of asthma comes from Kayser,⁴⁴ in which he extols its use in this and many other affections. His discussion of its action, however, fails to show its relationship to the nervous system and the ions in the peripheral cells.

Since we now know calcium to be an integral part of the cell and to be necessary to sympathetic nerve action, we have a basis for its use, founded on rational biological principles. By increasing sympathetic action in the neuromuscular mechanism of the bronchi, vagus action is depressed or inhibited, and if the action is sufficiently strong the asthmatic paroxysm is relieved. How long its action will last will have to be determined by further experience.

In asthma the action of calcium upon the cell results in the same physiological process as stimulation of the sympathetic nerves or the administration of adrenin. Adrenin heretofore has been the most successful remedy in the relief of paroxysms, but its disadvantage is that its action is of such short duration. From our present experience it is hoped that the action of calcium will be of much longer duration and that it may prove efficient in supplementing the action of adrenin and relieving the paroxysms for a longer time.

This same biological explanation serves to show how calcium exerts its beneficial effects in tuberculosis of the intestine, hay-fever, acute rhinitis, serum disease and other conditions which are accompanied by syndromes of parasympathetic hyperirritability. In tuberculous enteritis it increases sympathetic action which antagonizes the vagus and so relaxes the muscular tension and relieves the pain caused by it. By its relaxing effect on the musculature of the gut it may also improve diarrhea when present.

Recently, in a case of anaphylaxis caused by the injection of horse serum, we relieved the anaphylactic phenomena by an intravenous injection of 5 cc of a 5 per cent solution. We also have been able to improve the distressing symptoms of hay-fever by it. These various uses of it substantiate its general sympathicotonic nature.

The question of dosage is one which will require considerable attention. No doubt it is an individual matter, depending upon the degree of disparity between the sympathetic and the vagus tonus in the neuromuscular mechanism of the bronchi in each case.

Case Reports. CASE I.—Mrs. J. L. S., married, housewife, aged sixty-five years, entered the Pottenger Sanatorium, November 28, 1922.

Personal History. The patient suffered an attack of "grippe" thirteen years ago. There were no complications, but the patient was a long time recovering. For the last six years the patient has suffered from "colds" which were worse during the winter season. At first these colds were not accompanied by expectoration, but since the spring of 1921 a constant bronchial trouble with expectoration has been present, and the patient has been conscious of sounds in her chest that she describes as "moaning doleful sounds." The sputum at this time was "white" in color but not frothy, and contained numerous strings of inky-black particles. In November, 1921, she had a severe cold which aggravated all symptoms, but there were no distinct wheezes or whistles. The patient made a poor recovery from this attack and was "up and down" most of the winter. Sputum now changed to a dark gray. In April, 1922, the patient suffered the first real paroxysm of asthma, which lasted several hours. Following this the patient was very weak and remained in bed for some time. There was a continued wheezing character to the respiration, and this was worse at night. Added to the continuous bronchial disturbance, a distinct asthmatic paroxysm occurred about every two to three weeks. Up to this time the patient lived in Seattle. She came to Los Angeles on October 27, 1922. The asthma grew worse and the patient says continued all the time, until entering the sanatorium. Medication prior to entering the sanatorium consisted of steam inhalations and cough mixtures.

No history of any pulmonary trouble in the family.

Physical Findings. The patient lay in bed in a semi-recumbent position. She was cyanotic. Respiration was labored and pulse was rapid. She appeared weak and in distress.

Chest Findings. The respiratory note was almost obliterated by the asthmatic squeaks which were heard throughout both lungs. Numerous mucous rales were also present and a high-grade emphysema involved both lungs. The heart outline was enlarged and the sounds weak.

Except for the changes incident to age no abnormalities of the other systems were noted.

Laboratory Findings. Sputum: December 1: 10 cc in one day; 3 tubercle bacilli in ten minutes. December 14: 20 cc in one day; 1 bacillus in ten minutes.

Urine: Negative.

Blood: Hemoglobin, 92 per cent; white blood cells, 6100.

Roentgen-ray Findings. Some scarring throughout both lungs with dense hilus shadows that contain calcified nodes; no definite evidence of active pulmonary tuberculosis.

Medication. Adrenin, 1 to 1000, was given in 10-minim doses as needed to relieve the paroxysm. One dose per day was usually sufficient; occasionally two doses were given. The last dose of adrenin was administered sixteen days after entry. A total of twenty doses of 10 minims each were given. Calcium chloride (5 per cent in 5-cc doses) was given intravenously, starting November 29, and repeated every two to three days until three doses were given; then once a week for two weeks. The last dose of calcium chloride was given on December 20, twenty-three days after entry, making a total of five doses. There was a slight return of the wheezing on February 15, 1923, and one more dose of calcium chloride was given intravenously with complete relief. No return one month later.

Other therapeutic measures used were rest in bed, strychnine sulphate, several times daily for the first month, cough mixtures, as needed, and tuberculin in graduated doses. During this time only one hypodermic of morphine was resorted to.

Present Condition. March 12, 1923: The patient has been free from symptoms, except on February 15, since December 13, 1922. She feels much better. Her appetite and general appearance are much improved; respiration is free and easy; pulse-rate has fallen from 20 to 30 beats. She coughs up very little now, except a small quantity in the morning.

CASE II.—Mrs. A. W. H., aged forty-seven years, entered the sanatorium, January 29, 1923.

Personal History. In December, 1920, she moved from Idaho to Vancouver, B. C., at which time she caught a severe cold. The cough persisted and lasted for a period of two months. The condition at this time was diagnosed as asthma. Later she moved to Spokane, and the asthma still continued and paroxysms grow worse. The attacks averaged about four or five in the twenty-four hours. Adrenin was given for the attacks and many other medicines, including an asthma powder, were also administered. From December 20 until the middle of the summer of 1921 she was hardly free from asthma at any time. After two months' relief in August, 1921, paroxysms began again. From November, 1921,

to the end of January, 1922, the patient was treated by a diet low in protein and an autogenous vaccine, with apparent benefit. In the spring of 1922 she also began the use of adrenin, taking from 2 to 5 minims at a dose, which she continued as needed until February 11, 1923. After entering the sanatorium she received doses from 3 to 8 minims each night until February 11, after which no more was necessary. She also used antispasmodics by inhalation.

Since the asthma began, with the exception of the short period in the summer of 1921, she has not been free until now. On entering the sanatorium the patient was in a very high state of nervous excitement. Her physical condition was very much reduced. The lungs were filled with whistling and squeaking rales. Marked emphysema was present. The patient was extremely dyspneic, and walked with difficulty.

Laboratory Examinations. Sputum: Twenty-four-hour quantity, 65 cc; albumin, negative; bacilli, negative.

Urine: Negative.

Blood: Hemoglobin, 85 per cent; white blood cells, 6500.

After the examination was completed patient received the first dose of calcium, 5 cc of a 5 per cent solution, on February 3, 1923. The second dose of 5 cc was given three days after, on February 6. After this dose the patient felt considerable relief. The third dose was given on February 10, and was combined with 5 cc of a 50 per cent glucose solution. The patient noticed immediate relief following this third dose, and by the second day following her expectoration had been reduced to one-half its former amount. The fourth dose of 5 per cent solution was given four days later, February 14, after which expectoration still continued to decrease.

After the second dose the asthma was reduced to one attack a day. Since February 11 the patient has been entirely free from asthma. The patient says that she is now feeling the best and freest from asthma that she has been since it began two years ago, but that she lives in fear lest it return.

CASE III.—Mr. B. R., single, salesman, aged twenty years, entered the sanatorium, December 14, 1922.

Personal History. Asthma began in May, 1917, while the patient was at home in New York. The trouble was severe from the beginning and would last for months at a time. For days he would have constant wheezing and was forced to remain in bed. He was given amyl nitrite and stramonium cigarettes, but no adrenin at first. The paroxysms alternated with periods of comparative freedom for several weeks. The attacks usually preceded and lasted during inclement weather. The patient was at a tuberculosis sanatorium at Loomis, New York, for about one year, and while there was given rest treatment and, during the latter part of his stay, adrenin, hypodermatically. Of this he

received from eighteen to twenty doses of 3 to 5 minims per day. In September, 1919, he went to Albuquerque and contracted typhoid fever in October, but recovered by January, 1920. During this illness he was free from asthma. All skin tests for protein sensitization were negative. He was given sodium cacodylate, about 5 hypodermics of adrenin per day, and dietary management. He felt much better during his stay in Albuquerque than in New York.

This patient went to Colorado Springs in March, 1920. The treatment was practically the same, but the asthma was more severe. Here he was given sodium cacodylate, iodides and a vaccine prepared from sputum cultures. The skin tests repeated here were negative.

Mr. R. came to Southern California in March, 1921. The iodides, sodium cacodylate and adrenin were continued. Pituitary extract by mouth was also given, but with no appreciable effect. In spite of his condition the patient went to work in August, 1922, as a salesman, demonstrating electrical appliances. He was taught how to use adrenin himself, and carried a supply with him and administered on the average about five doses daily. After four months he was forced to quite work on account of the severity of the paroxysms, which were now almost constant, except when relieved by adrenin. Adrenin was the only medication that gave him relief and he resorted to its hypodermic use from fifteen to twenty-five times a day, taking a total of 5 to 7 cc of a 1 to 1000 solution daily. All this time the sputum was persistently negative for tubercle bacilli.

Physical Findings. Aside from signs of healed tuberculosis and findings directly connected with asthma, such as an emphysematous chest, squeaking and whistling rales, no abnormalities were noted on auscultation.

Laboratory Findings. Sputum: Quantity, 100 cc a day; negative for tubercle bacilli.

Urine: Negative.

Blood: Hemoglobin, 90 per cent; white blood cells, 12,500.

Roentgen-ray Findings. Scarring in both upper lobes with thickening of the bronchial branches throughout. Slight haziness in right apex on the level of the first interspace, indicative of an old tuberculous lesion.

Medication. On entry the patient was taking a hypodermic of adrenin every hour or two during the entire day. Intravenous medication of calcium chloride was resorted to. At first only 5 cc were given and repeated every other day. After the first ten days the interval was lengthened to four and five days with 10 cc doses and finally to one dose a week. He has received a total of fourteen doses in the first two months' treatment and is free from paroxysms. Tuberculin in graduated doses was also given. The

other medication resorted to was atropine, supplemented by morphine for a few days shortly after entry. The adrenin treatment was continued, but in decreasing number of doses, until February 21. Prior to this time he had periods of twenty-four to thirty-six hours, when no adrenin was necessary. During his stay at the sanatorium he developed an acute respiratory infection with a rise in temperature to 100° and 102° F., lasting for several days. During this time he was entirely free from asthma both in signs and symptoms.

Discussion. The three cases here detailed are not enough to bring out the many difficulties that will have to be overcome in order to establish the definite part that calcium plays in the relief of the paroxysms of asthma. They are sufficient, however, to show that calcium influences the neurocellular mechanism in the manner that is necessary to the control of such paroxysms. They offer the opportunity of discussing and illustrating the ionic control of tissues and showing its relationship to the visceral nerves in a disease which has been difficult to understand and equally difficult to treat.

These cases illustrate three different types of asthma. The first and second are types which follow attacks of bronchitis. The specific element which precipitates the paroxysms in these cases was most probably bacterial in nature. It is interesting to note that the administration of calcium relieved both the bronchial spasm and the bronchial secretion. This is what would be expected from the physiological control of these tissues, since both musculature and secreting glands are activated by the vagus nerve and inhibited by the sympathetics, with which calcium works in harmony. I was not prepared, however, to expect so prompt and rapid a reduction as occurred.

The relief of heart strain with slowing of the pulse in the first case was almost phenomenal. While stimulation of the sympathetic nerves under ordinary circumstances accelerates the pulse, under the circumstances which relieve these asthmatic paroxysms it slows it, showing that the dyspnea and rapid heart in asthma are not a part of the true asthma syndrome, but a result of the mechanical interference with respiration caused by the overstimulation of the bronchial structures which results in narrowing of the tubes. The slowing of the pulse which takes place when calcium, a sympathicotonic salt, is administered may be looked upon as affording a definite proof of favorable action upon the bronchial structures.

The third case may also be of bacterial origin, but this has not been proved from sensitization tests. The patient has never reacted to any tests administered. His paroxysms may be due to some reflex cause which still remains undetermined. Asthma can be

caused reflexly by stimuli arising in any structure in the body which is supplied by sensory nerves which mediate with the motor nerves of the pulmonary branches of the vagus thus: (1) All viscera supplied with sensory nerves by the vagus; (2) those structures in the head which are supplied by the sensory fibers of the fifth cranial nerve, for the sensory branches of the fifth mediate readily with the vagus; (3) other structures found in distant parts of the body, such as the pelvis, where afferent sensory nerves are connected by intercalated neurons which carry the impulse the entire length of the cord and mediate with the vagus. The question of finding the organ or tissue from which reflexes, capable of exerting the paroxysms of asthma, arise may offer many difficulties when no evident inflammatory process is present.

One very interesting phase of the treatment in this case was the enormous amount of adrenin which the patient had used over a long period of time. This patient was much more difficult to relieve than the others. I thought of a possibility which must always be kept in mind in connection with visceral nerve action, viz., that of reverse or transferred action.³³ Sometimes when the neurons belonging to a given system become very hypersensitive a stimulation, which, under ordinary circumstances, would act on that system and produce an action or inhibition of action in certain tissues, produces the reverse. This may be due to the neurons having reached a condition in which they can no longer respond or the stimulus being transferred to the antagonistic system. Changes in the ionic content of the cell may also be a cause of such unexpected reaction.

The fact that he responded so slowly made me think that possibly the long use of adrenin in such large quantities had so sensitized his sympathetic mechanism that when an extra stimulation of the sympathetic neuromuscular mechanism was produced by the introduction of calcium ions, instead of causing an increased sympathetic action, the neurons responded but feebly and consequently the relief was only partial. By persisting, however, we were able to give complete relief.

The suggestion in this paper have nothing to do with those aspects of the study of asthma which attempt to find the exciting causes, but represent an attempt to interpret the ultimate reactions in the body in terms of physiology, biochemistry and biophysics, so as to afford some definite concept of the departures from normal in nerve balance and ion equilibrium of the cells, which are responsible for the asthmatic paroxysm. It opens up many questions for investigation. It emphasizes strongly that in our investigations of problems in visceral neurology we must have in mind a cellular as well as a neurological concept and think in terms of the entire neurocellular mechanism.

Conclusions. 1. Bronchial asthma is a condition in which the neuromuscular mechanism of the bronchial system is in a state of hyperirritability.

2. This hyperirritability shows itself as an increased action on the part of the bronchial divisions of the vagus nerve of the parasympathetic system. According to the studies here cited, the action of the vagus depends upon the presence of potassium, and increased vagus action depends upon a preponderance of potassium ions as compared with calcium ions in the bronchial tissues.

3. Inasmuch as the activity of the vagus nerve which belongs to the parasympathetic system is antagonized by the sympathetic nerves, and inasmuch as a relative increase in the calcium ions produces the same effect as sympathetic stimulation, the administration of calcium is a rational therapeutic measure in combating asthmatic paroxysms.

4. Calcium therapy has a rational basis in other conditions which are accompanied by hyperirritability of the parasympathetic system, such as asthma, hay-fever, urticaria, serum disease, spastic colon and diarrhea.

BIBLIOGRAPHY.

1. Huber, Harry L. and Koessler, Karl K.: The Pathology of Bronchial Asthma, *Arch. Int. Med.*, 1922, 30, 689.
2. Brown, Orville, Harry: Asthma, C. V. Mosby Co., St. Louis, 1917.
3. Babcock, R. H.: Spasmodic Asthma, *Jour. Am. Med. Assn.*, 1917, 68, 738.
4. Walker, I. Chandler: Cause and Treatment of Bronchial Asthma, *Jour. Am. Med. Assn.*, 1917, 69, 363.
5. Walker, I. Chandler: A Clinical Study of Bronchial Asthma, *Boston Med. and Surg. Jour.*, 1918, 179, 288.
6. Rackemann, Francis M.: Study of Cause of Bronchial Asthma, *Arch. Int. Med.*, 1918, 22, 577.
7. Rackemann, Francis M.: Clinical Classification of Asthma Based on a Review of Six Hundred and Forty-eight Cases, *AM. JOUR. MED. SCI.*, 1921.
8. Cooke, Robert Anderson: Hay-fever and Asthma, *New York Med. Jour.*, 1918, 107, 577.
9. Cooke, Robert Anderson, and Vander Veer, Albert: Human Sensitization, *Jour. Immunol.*, 1922, 1, 201.
10. Wolff-Eisner, A.: Das Heufieber, sein Wesen und seine Behandlung, München, 1906.
11. Blackfan, Kenneth D.: A Cutaneous Reaction from Proteins in Eczema, *Am. Jour. Dis. Child.*, 1916, 11, 441.
12. Scheppegegrell, William: Hay-fever and Asthma, Lea & Febiger, Philadelphia, 1922, p. 119.
13. Piness, George: Modern Aspects of the Etiology and Treatment of Bronchial Asthma, *Northwest Med.*, 1923, 22, 1.
14. Godall, E. W.: Serum Sickness, *Jour.-Lancet*, March 2, 1918, p. 323; March 9, 1918, p. 361.
15. Wells, H. Gideon: The Present Status of the Problems of Anaphylaxis, *Physiol. Rev.*, 1921, 1, 64.
16. Pottenger, F. M.: Symptoms of Visceral Disease, C. V. Mosby Co., St. Louis, 2d Edition, 1922.
17. Pottenger, F. M.: Asthma Considered in its Relationship to the Vegetative Nervous System, *AM. JOUR. MED. SCI.*, 1918, 155, 417.

18. Pottenger, F. M.: Clinical Tuberculosis, C. V. Mosby Co., St. Louis, 2d Edition, 1922, 2, 166.
19. Moore, Benjamin: Biochemistry, Edward Arnold, 1921, p. 11.
20. Ringer, Sydney: Concerning the Influence Exerted by Each of the Constituents of the Blood on the Contraction of the Ventricle, Jour. Physiol., 1880-1882, 3, 380.
21. Ringer, Sydney: A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, Jour. Physiol., 1883, 4, 29.
22. Ringer, Sydney: A Third Contribution Regarding the Influence of the Inorganic Constituents of the Blood on the Ventricular Contraction, Jour. Physiol., 1883, 4, 222.
23. Howell, W. H.: Vagus Inhibition of the Heart in its Relation to the Inorganic Salts of the Blood, Am. Jour. Physiol., 1906, 15, 280.
24. Howell, W. H. and Duke, W. W.: The Effects of Vagus Inhibition on the Output of Potassium from the Heart, Am. Jour. Physiol., 1908, 21, 51.
25. Zondek, S. G.: Untersuchungen über das Wesen der Vagus und Sympathikus-erregung, Berl. klin. Wchnschr., 1921, 58, 1393; and Deutsch med. Wchnschr., 1921, 47, 1520; 1541.
26. Kraus, F. and Zondek, S. G.: Preliminary Report on Experiments on the Role of Electrolytes in the Heart Beat, the Effect of Salt in Hemorrhage and the So-called Tonus Current, Klin. Wchnschr., Berlin, 1922, 1, 996.
27. Abderhalden, Emil: The Nature of Innervation and its Relation to Internal Secretion, Klin. Wchnschr., 1922, 1, 7.
28. Kolm, R. and Pick, E. P.: Ueber die Bedeutung des Calciums für die Erregbarkeit der Sympathischen Herz-Nervenendigungen, Arch. f. d. ges. Physiol., 1921, 189, 137.
29. Andrus, E. C. and Carter, E. P.: Effect upon Cold-blooded Heart of Changes in Ionic Content of Perfusate: I. Upon Normal Mechanism; II. Upon Arrhythmias, Am. Jour. Physiol., 1922, 59, 227.
30. Daly, I. de B. and Clark, A. G.: Action of Ions upon Frogs' Hearts, Jour. Physiol., 1921, 54, 367.
31. Hammett, F. S.: The Role of the Change in Hydrogen-ion Concentration in the Motor Activities of the Small Intestine, Am. Jour. Physiol., 1922, 60, 52.
32. Loewi, O.: Humoral Transmissibility of Cardiac Nerve Activity, Arch. f. d. ges. Physiol., 1921, 193, 201.
33. Sollmann, Torald: The Pharmacology of the Autonomic System, Physiol. Rev., 1922, 2, 479.
34. Longcope, W. T. and Mackenzie, George M.: Anaphylaxis, Hypersensitivity and Protein Intoxication, Endocrinology and Metabolism, 1922, D. Appleton & Co., vol. 4, p. 197.
35. Besredka, A.: Anaphylaxis and Anti-anaphylaxis, Eng. Edition translated by Gloyne, St. Louis, C. V. Mosby Co., St. Louis, 1919.
36. Zinsser, Hans: The More Recent Developments in the Study of Anaphylactic Phenomena, The Harvey Lectures, J. B. Lippincott Co., Philadelphia, Series X, 1914-1915, p. 177.
37. Pearce and Eisenbrey: Tr. Congr. Am. Phys. and Surg., 1910, 8, 402.
38. Coca, A. F.: Ztschr. f. Immunitätsforsch., 1914, 20, 622.
39. Schultz, W. H.: The Reaction of Smooth Muscle in the Guinea-pig, Sensitized with Horse Serum, Jour. Pharmacol. and Exper. Therap., 1910, 1, 549.
40. Dale, H. H.: The Anaphylactic Reaction of Plain Muscle in the Guinea-pig, Jour. Pharmacol. and Exper. Therap., 1913, 4, 167.
41. Weil, R.: Jour. Med. Research, 1913, 27, 497; 1914, 30, 87; 299, Proc. Soc. Exper. Biol. and Med., 1914, 11, 86.
42. Eppinger and Hess: Die Vagotonie, Samml. klin. Abhandl., von Noorden, 1910, Nos. 9 and 10.
43. Meyer, Hans H. and Gottlieb, R.: Die Experimentelle Pharmakologie, 1921, Urban & Schwarzenberg, Berlin.
44. Kayser, Curt: Wratsch, Berlin, October 15, 1922, p. 453.

A CASE OF ACQUIRED CHRONIC HEMOLYTIC (ACHOLURIC) JAUNDICE, SEEN FIFTEEN YEARS AGO WITH A BLOOD-PICTURE AT THAT TIME RESEMBLING ONE OF PERNICIOUS ANEMIA.

BY F. PARKES WEBER, M.A., M.D., F.R.C.P.,

LONDON, ENGLAND.

Case History. The patient is a woman, now aged fifty-three years, who was first admitted to hospital under my care in January, 1908, when she was thirty-seven years of age.¹ According to the history given at that time she had been healthy until three years previously, when she commenced to look pale. About a year later she had an attack of jaundice, with pains in the right side; afterward she gradually became weaker and paler and short of breath on exertion. Menstruation became scanty, and for a time there was complete amenorrhea. She suffered from recurrent epistaxis and was troubled with coldness and numbness of the hands and feet; sometimes there was a sensation of "pins and needles" in the fingers, which would "go blue."²

After admission to hospital in January, 1908, the condition noted was the following: The skin and conjunctivæ were yellowish. There was no pruritus or xanthoma. The legs were edematous. The heart seemed slightly dilated, and there was a faint systolic murmur, apparently not due to valvular disease. The liver and spleen were both evenly enlarged. The liver extended two or three fingers' breadth below the ribs, and the spleen, which was hard, reached almost to the anterior-superior iliac spine. The condition of the patient's mouth was not bad, though she had lost many of her teeth. Occasionally there was slight bleeding from the gums. Attacks of epistaxis were frequent. Ophthalmoscopic examination (Dr. C. Markus) showed numerous bright red, round, retinal hemorrhages in both eyes, chiefly in the upper halves of the fundi. The urine of specific gravity 1013, contained albumin (1 per mille by Esbach's tube on admission), but no tube casts. A later note of the urine stated it to be of specific gravity about 1015, of deep orange color, free from albumin and sugar, and giving no Gmelin's reaction for bile pigment, but containing

¹ I showed the case at the Medical Society of London on April 13, 1908, February 8, 1909, and January 27, 1913 (*Trans. Med. Soc. Lond.*, 1913, 36, 360). I also described the case in full in the *AM. JOUR. MED. SCI.*, Philadelphia, 1909, 138, 24, and published a sequel in the *Practitioner*, London, 1913, 90, 811. The patient was shown on May 29, 1923, at the Medical Section of the Royal Society of Medicine, London.

² I would here note that even more decided nervous troubles and actual combined degeneration of the spinal cord may occur not only in pernicious anemia, but also in various anemic and cachectic conditions. Salomon (*Gesellsch. f. inn. Med. u. Kinderheilk. zu Wien*, January 29, 1914) showed a man, aged thirty-two years, with hemolytic jaundice and combined degeneration of the spinal cord.

excess of urobilin. The feces were never acholic. Examination of the gastric contents after a test-breakfast (May, 1908) showed complete absence of free hydrochloric acid.

Examination of her blood on January 31, 1908, gave the following result: Hemoglobin (by Haldane's method), 18 per cent of the normal; red cells, only 900,000 in 1 cm. of blood; white corpuscles, 6000; color index, 1. The differential count of the white cells gave: Lymphocytes, 45.6 per cent; transitionals, 4.8 per cent; large mononuclears, 2.4; neutrophile polymorphonuclears, 46; eosinophiles, 0.8; mast cells, 0.4. During the count of 500 white cells Dr. A. E. Boycott saw no ordinary normoblasts, but 8 typical megaloblasts (gigantoblasts) of the pernicious anemia type and 16 smaller nucleated red cells, resembling the typical megaloblasts except in regard to their relatively small size. There were a few polychromatophilic red cells and many punctate basophilic red cells. Decided anisocytosis and poikilocytosis were present, as in pernicious anemia. The blood picture at that time was one of typical "megaloblastic degeneration"—I would prefer to say "megaloblastic regeneration" or "megaloblastic regenerative reaction"¹—but a striking feature was the association of chronic acholuric jaundice, and the case likewise differed from pernicious anemia in regard to the enlargement of the spleen and liver. I regarded the case at first as a variety of pernicious anemia with unusual enlargement of the spleen and liver, but afterward I came to the conclusion that it was one of acquired chronic hemolytic (acholuric) jaundice, with gastric achlorhydria and a blood picture suggestive of pernicious anemia. The resistance of the patient's erythrocytes to hemolysis, as tested with graduated hypotonic sodium chloride solutions, was less than that in various healthy persons used as controls.

In the treatment of the case the arsenical preparation known as atoxyl was especially employed; but the great improvement which ultimately followed, could not with certainty be attributed to the atoxyl, as the period of the most decided improvement commenced a considerable time after the atoxyl treatment had been discontinued.

In December, 1908, the blood showed nothing abnormal beyond slight anemia. She became free from jaundice, fever and edema. The liver could no longer be felt enlarged. The retinal hemorrhages cleared up. The condition remained fairly good, and the patient was able to do ordinary work as a domestic servant. On July 17, 1911, the red cells numbered 5,330,000 to 1 cm. of blood.

Discussion. Several features of the patient's illness up to the summer of 1909 require special mention and consideration.

¹ That is to say, the blood picture of so-called "megaloblastic degeneration" must be interpreted as representing an automatic attempt at regeneration.

Abdominal Pain. At various times the patient complained of pain or tenderness in the upper part of the abdomen, sometimes in the region of the liver, sometimes associated with fever. An attack about the middle of August, 1908, was associated with vomiting and temporary increase of the icteric tinge; a short attack in December, 1908, was accompanied by a sudden rise of temperature to 103° F. Attacks of this kind are well known in hemolytic jaundice and represent temporary exacerbations of the disease. They may be mistaken for attacks of cholelithiasis, and actual gall stones have been found in some cases.

Jaundice. While under observation the patient was never deeply jaundiced, but the conjunctivæ for a long while were distinctly yellow. With the improvement in the general condition in November, 1908, the jaundice disappeared. With a single doubtful exception (during a temporary exacerbation of the jaundice), bile pigment was never present in the urine; the feces were never acholic.

Temperature. At first there were recurrent periods of moderate fever, but after September, 1908, there was hardly any fever. On December 13, 1908, a temperature of 103° F. was noted in association with abdominal pain (see back, under *abdominal pain*).

About June, 1912, the patient commenced to suffer from interstitial keratitis of the right eye, which was evidently regarded at an eye-hospital as of syphilitic origin. When seen at the end of 1912 and in the early part of 1913 she was slightly anemic, but microscopical examination of blood films showed nothing abnormal. There was no excessive fragility of the erythrocytes toward hypotonic saline solutions. The liver was apparently not enlarged. The spleen could just be felt below the costal margin. The conjunctivæ had a slight yellowish tinge and the urine (December, 1912) showed some excess of urobilin. Her blood serum on one occasion (January, 1913) gave a positive Wassermann reaction, but on two other occasions about that time it gave a negative Wassermann reaction.

On May 8, 1923, the patient was re-admitted under my care, with the history that since I last saw her in 1913 she had remained in good health until the end of 1922, when, possibly as a result of excessive work (as a monthly nurse, cook, etc.), she commenced to suffer from a feeling of weakness, a tendency to cardiac palpitation and giddiness on exertion; she had also noticed pallor and yellowness of her face. The menopause had occurred about 1921, when she was fifty-two years of age. On re-admission I find her looking obviously anemic, with light icteric coloration of her skin and sclerotics. The spleen is moderately enlarged and the liver (not very hard to palpation) reaches down to the umbilical level. The temperature is occasionally very slightly raised; pulse, 66 to 80; respiration, 16 to 20; brachial systolic blood-pressure, 115 to

140 mm. Hg. The fundi of the eyes appear normal, but there are posterior synechiæ in the right eye from earlier plastic iritis (Dr. C. Markus). The gastric contents after a test-breakfast show complete absence of free hydrochloric acid and of pepsin (achylia gastrica). The blood serum (May 10, 1923) gives a completely negative Wassermann reaction. The feces are if anything rather deeper colored than average feces. The urine is of a reddish-orange color, free from albumin, sugar and bilirubin, but showing excess of urobilin and urobilinogen. It is free from bile acids, according to surface tension estimations by Dr. J. W. McNee and Mr. E. A. B. Pritchard.

For the present blood examinations I am indebted to Dr. G. Welsch. The blood-count (May 9, 1923) gives: Erythrocytes, 1,800,000 per 1 cm. of blood; hemoglobin, 40 per cent; color index, 1.1; white cells, 6100 per 1 cm. of blood. The differential count of 300 white cells gives: Neutrophile polymorphonuclears, 74 per cent; lymphocytes, 24.5 per cent; no transitionals or large mononuclears; mast cells, 1.5 per cent; no eosinophiles. In regard to the red cells there is much anisocytosis; the macrocytes are especially numerous and show polychromatophilia and decided poikilocytosis. While making the differential count of white cells 3 nucleated red cells were observed; 2 of these were normoblasts with polychromatophilic cytoplasm, and the other was a large megaloblast with a large ("loose") nucleus and polychromatophilic cytoplasm. The resistance of the erythrocytes toward hemolysis was estimated (May 10, 1923) by adding drops of the whole blood to graduated hypotonic sodium chloride solutions. The hemolysis was found to commence with a 0.52 per cent solution and to be complete with 0.42 per cent solution. The resistance of the erythrocytes is therefore definitely below the normal standard; that is to say, their fragility is somewhat excessive, as it is in cases of congenital and acquired hemolytic jaundice.

Dr. J. W. McNee (June 1, 1923) kindly examined the blood for bilirubin and bile acids. The blood serum was yellowish and opalescent (physiological lipemia, owing to a recently taken meal). It gave a negative *direct*, but a positive *indirect* Hijmans-van den Bergh reaction for bilirubin, equivalent to $5\frac{1}{2}$ van den Bergh units (or 1 in 36,364). It was free from bile acids, according to surface tension estimations (Mr. E. A. B. Pritchard).

The case is one of hemolytic (acholuric) jaundice, apparently acquired. The old plastic iritis and interstitial keratitis in the right eye suggests that the patient may likewise have had syphilis. I have recently examined her only living child, a sailor, aged twenty-five years, who appears to be healthy and presents no signs of hemolytic jaundice or syphilis. After the birth of that son she never became pregnant again, but before his birth she now tells me that she had: (1) A female child, who died at twenty-one

months of "convulsions;" (2) a miscarriage; (3) a still-born child.

At first, in January, 1908, I temporarily mistook the case for one of pernicious anemia, and it is interesting to note that the blood picture now again (May, 1923) is of the pernicious-anemia type. In cases of congenital hemolytic jaundice poikilocytosis is usually not a feature of the blood picture, but there is generally great anisocytosis, with predominance of *apparent microcytes*. These "*microcytes*" are not true microcytes, as they are not really small; they have been shown by Naegeli and others to be only apparently small, because they have a relatively small diameter and a relatively small circumference; but, in regard to their total volume, they are really large, owing to their globular or ball-like shape ("Kugelzellen"). In some cases of hemolytic jaundice (especially acquired cases) like the present one there seems to be a tendency for the blood picture, during exacerbations of the disease, to assume the "pernicious anemia type," with poikilocytosis and megaloblasts, and with predominance of "macrocytes," instead of the ball cells ("Kugelzellen") of Naegeli.

It is possible that the patient's present exacerbation may be due to excessive work and fatigue. In regard to the injurious influence of mental strain and physical fatigue in cases of hemolytic jaundice, I may mention that one of the family (Ernest T.) of congenital hemolytic jaundice reported by Dr. Dorner and myself in 1910,¹ who was at that time twelve years of age and only slightly affected, had later on to undergo great strain as an artilleryman during the World War. Under the strain, after a considerable time, he broke down with an exacerbation of the disease. He became extremely anemic and his splenomegaly greatly increased, as Dr. J. H. Drysdale kindly showed me in St. Bartholomew's Hospital, where splenectomy was successfully performed in 1922. That patient's paternal grandfather, though jaundiced all his life, lived to seventy-six (not seventy years, as, owing to an error in copying, we stated in the account published in 1910), and both this and other published data proved that patients with hemolytic icterus may sometimes under ordinary circumstances live to a good age like normal persons, even though splenectomy is never performed.

The good results obtained by splenectomy (when successfully performed) in cases of hemolytic icterus seem to be due not only to the removal of the acknowledged hemolytic action of the spleen, but likewise to the removal of some subtle influence of the spleen on the bone-marrow in these cases, owing to which influence the bone-marrow produces abnormal erythrocytes with low resistance toward hemolysis. It is reasonable to suppose that the excessive hemolysis, caused by the presence of defective erythrocytes, leads

¹ Weber, F. Parkes and Dorner, G.: "Four Cases of Congenital Acholuric (Hemolytic) Jaundice in One Family," *Lancet*, London, 1910, 1, 227.

to increased production by the bone-marrow of the defective type of erythrocytes in question — a “vicious circle,” which to some extent can be “broken” by splenectomy.

Summary. A case of acquired chronic hemolytic anemia which was first seen fifteen years ago is reported together with a discussion of the injurious influence of mental strain and physical fatigue in cases of hemolytic jaundice, and the difficulty of the differential diagnosis in some cases from pernicious anemia.

THE DIAGNOSIS AND MANAGEMENT OF SUPRAVESICAL HEMATURIAS.*

BY PAUL W. ASCHNER, M.D.,

ADJUNCT ATTENDING SURGEON AND ASSISTANT IN SURGICAL PATHOLOGY,
MT. SINAI HOSPITAL, NEW YORK.

(From the Surgical Service of Dr. Edwin Beer.)

It would seem hardly necessary to reiterate the importance of regarding every case of hematuria as one of grave possibilities until proven otherwise. It is surprising for how long a time a patient will pass bloody urine without attaching significance to it. It is still more surprising how often the first physician consulted will prescribe a diet and medication after a cursory general examination and urinalysis. The bleeding ceasing, as it often does of its own accord, both patient and doctor are lulled into a false sense of security.

If neoplasms of the urinary organs are to be detected early enough to improve our therapeutic results, patients with hematuria must be given the benefit of a prompt and complete urological examination. The important indication is to determine the source of the bleeding by cystoscopical observation, and, as a rule, the time to do so is when the patient is passing bloody urine. If the cause of the bleeding is in the bladder or urethra the diagnostic problem is relatively simple, but if the lesion is in the kidney or ureter the problem is frequently complex. In the latter case the actual source of the bleeding is not visible and the diagnosis must be arrived at by deduction and processes of exclusion. A certain routine had best be followed if accuracy is to be attained and errors avoided.

A careful history and physical examination may give important leads. For example, a recent attack of tonsillitis or scarlatina should make us suspect a focal infectious nephritis. A history of

* Read before the Eastern Medical Society, New York Academy of Medicine, April 13, 1923.

preceding attacks of renal colic not associated with hematuria suggests calculus. As the passage of blood clots, pieces of tissue, leukoplakic membrane or fibrinous exudate may cause severe colic, the occurrence of pain during the period of hematuria is not of differential value. Frequency and urgency of urination necessitate the careful exclusion of tuberculosis.

An enlarged kidney indicates hydronephrosis or tumor. Bilateral nodular renal enlargement suggests polycystic kidneys. Disease of the heart, lungs, or vessels which may cause circulatory disturbances are worthy of attention. Many other examples will suggest themselves.

In the examination of the urine, pus, casts, bacteria and tubercle bacilli in association with the blood should be carefully looked for. Epithelial and red blood cell casts indicate a nephritic origin for the hematuria. Pus may be present in cases of calculus, and always in tuberculosis and bacterial infections. But it must be remembered that the presence of nephritis, of calculus or of infection does not exclude the possibility of an associated tumor.

The cystoscopical observation of the bladder then determines whether the bloody urine is coming from one or both ureters. This point separates at once the bilateral hematurias, which have a constitutional or systemic etiology, from the unilateral hematurias which usually have a local pathological condition underlying them. The bladder itself may be perfectly normal in appearance, but in some cases lesions are present which give evidence of what sort of pathology exists in the kidney or ureter. The ureteral catheters are now introduced a short distance, and specimens are collected for microscopical examination, urea content and bacteriology. The catheters are then advanced and specimens collected at the middle and upper levels, if no obstruction is encountered. As to further methods of examination one is guided by the findings thus far obtained, and they will be considered in connection with the various groups of cases to be described.

Paroxysmal Hemoglobinuria. This rather rare disease is chiefly of interest to the internist.

It occurs more frequently in men than in women, and may occur in children. It is characterized by a prodromal period of malaise and nausea, then a chill followed by high temperature and sweating, pains in the muscles and back, itching of the skin, and at times urticaria. The urine voided during the attack, and for a few days thereafter, has a dark brown bloody color. The attack is brought on by exposure to cold and wet, and can readily be induced by immersion of the hand or foot in iced water. The disease has a luetic basis and a specific hemolysin is present in the blood, whose action was demonstrated *in vitro* by Donath and Landsteiner. The urine contains but few formed elements, the color being due to the presence of hemoglobin. Casts and leuko-

cytes may be present. Although as one would expect, the hemoglobinuria is bilateral, a case of unilateral hemoglobinuria was reported by Fleckseder.

Bilateral Hematurias Due to Nephritis. Included in this group are the cases of macroscopical hematuria in which the bleeding occurs from both kidneys simultaneously as demonstrable by cystoscopy. (The subject of unilateral nephritis will be discussed later.) Many cases of nephritis show more or less blood in the urine, particularly the acute and subacute forms, but only a few types are of interest here.

There are cases of *subacute hemorrhagic nephritis* in which hematuria is the presenting or sole symptom. This type of case is seen by the urologist because the usual manifestations of nephritis are absent. For example, a man, aged forty-six years, had bloody urine for four months. At first it was slight but it persisted and increased. There was no pain, urgency or frequency. Aside from loss of weight (10 pounds), and recently slight headache, there were no symptoms. The urine had been examined many times and nothing but blood reported. Physical examination was negative. Roentgen-ray of the urinary tract was negative. The blood-pressure was 145 systolic and 90 diastolic. Cystoscopy showed bloody efflux from both ureters and the ureteral specimens were of a uniform color at all levels on both sides. But on careful examination red blood cell casts were seen and this made the diagnosis of nephritis certain. Cultures proved sterile.

A number of interesting cases of *focal infectious nephritis with hematuria* have been observed both on the medical and urological services. They are almost exclusively of tonsillar origin, although in one case infection of the upper respiratory tract and in another furunculosis due to scabies were the exciting causes. The disease may be ushered in by a chill and fever and sore throat. In a few days the patient notices frequency, urgency and dysuria, pain in one or both flanks and the passage of bloody urine. A history of previous attacks may be elicited. In some cases the patient complains of nothing but bloody urine and it is only by close questioning and careful examination that the tonsillar origin of the trouble is detected. The cases occur chiefly in young and middle-aged individuals. A disproportion between the clinical well-being of the patient and the impairment of renal function is often observed. Thus the phenolsulphonephthalein excretion may be as low as 10 or 15 per cent, and the blood-nitrogen figures increased three or four fold. The blood-pressure too may be considerably elevated. The urine of these patients usually contains granular casts and leukocytes in addition to the blood. On cystoscopical examination the bladder may show no lesion, but in a few cases seen early in the disease punctate hemorrhages were observed in the trigone and larger submucous hemorrhages near the ureteral orifices. In most instances the same kind of urine flowed from the

two kidneys, and the output of indigo-carmin was equally delayed. *In all but two cases cultures of the ureteral specimens proved sterile.* The two exceptions were cases seen with Dr. Libman and Dr. Poll, in which an unusual amount of pus was present in the urine, with unusually severe vesical symptoms and a febrile course. Cystoscopy showed a diffuse cystitis, bilateral hemorrhagic nephritis and left-sided pyelitis due to *Bacillus coli*.

These cases have been treated by rest and dietetic regulation until the acute process has subsided. Tonsillectomy under local anesthesia has then been performed and with excellent results. In several cases the tonsillectomy was followed by lumbar pain and hematuria, a focal reaction seen similarly in tonsillectomy for arthritic conditions.

FURTHER METHODS OF EXAMINATION. In cases of unilateral hematuria any or all of the following methods should be employed in addition to the first cystoscopical examination.

1. Roentgen-ray examination.
2. Roentgen-ray examination with the opaque catheter and the injection of opaque media.
3. The wax-tipped catheter or bougie.
4. The use of the ureter catheter to detect an obstructing lesion, to induce or aggravate bleeding by manipulation, to collect material for histological examination.
5. Comparative functional tests.
6. Therapeutic tests.

The following causes of unilateral hematuria require consideration:

1. Trauma.
2. Calculus in the kidney or ureter.
3. Tuberculosis of the kidney and ureter.
4. Ureteritis and pyelitis cystica.
5. Stricture of the ureter.
6. Hydronephrosis.
7. Primary tumors of the ureter and kidney pelvis.
8. Tumors of the kidney parenchyma.
9. A group of various degenerative, inflammatory and vascular lesions both in and around the kidney, usually classified as cases of "essential hematuria."

Trauma. When bleeding of large proportions follows a slight injury one must bear in mind the possibility of a predisposing pathological condition. For example, a young man had been struck a blow in the left flank during a scuffle. One hour later he passed bloody urine. After three days of persistent hematuria he entered the hospital. Cystoscopy showed a left renal hematuria, and roentgen-ray showed a mass of stones in the kidney. The organ was removed and a bleeding ulcer was found due to the impaction of a sharp stone against the wall of the pelvis.

A hospital employee struck his left flank against the corner of a table. He resumed his work in a few minutes but soon afterward passed bloody urine. Cystoscopical examination gave evidence of a left hydronephrosis, which was confirmed by pyelography. The bleeding stopped in a few days.

When we consider how frequent calculus and tuberculosis of the upper urinary tract are, it is remarkable how seldom they are accompanied by macroscopical bleeding.

Calculus. A stone in the kidney or ureter may cause repeated attacks of hematuria with or without accompanying colic. The roentgen-ray will show the stone in about 90 per cent of cases. Phleboliths and calcified glands may produce confusing shadows, which must be properly identified by use of the opaque catheter and the injection of opaque media. Stereoscopical plates or two exposures on the same plate at different angles are desirable in these doubtful cases. The stones not visualized by the roentgen-ray (10 per cent) are usually uric acid stones. They may appear as negative shadows when opaque media are injected. Occasionally they may be impregnated with argyrol and thus made visible. By using a wax-tipped bougie or catheter a scratch mark may be obtained by contact with a stone. In the ureter this is a fairly reliable test, but if a stone is tucked away in a renal calyx, or covered with a fibrinous exudate the wax bulb does not always come in contact with it. Thus where a renal calculus is suspected a negative test has no value. In the ureter, however, a negative wax tip in the presence of an obstructing lesion is valuable. A positive scratch mark, with proper technic, constitutes good evidence of a calculus.

Tuberculosis. Cystoscopical observation gives much assistance in the diagnosis of this disease; tuberculous vesical ulcers, miliary tubercles at the ureteral ostium, and above all retraction and rigidity of the orifice. The cases with ureteral stenosis cause the most difficulty, for the bladder may show no lesions except the retraction of the orifice; the urine may show no bacilli; a catheter cannot pass the obstruction; and *the roentgenograms are very apt to show areas of calcification in the kidney, suggesting calculus to the unwary.* A negative test with the wax-tipped bougie passed to the obstructing lesion is valuable in excluding ureteral calculus. One may succeed in passing with the bulb, and on withdrawal it will be found deformed but not scratched. Inoculation of guinea-pigs with the ureteral specimens may clarify the diagnosis in obscure cases in which bacilli are not found in smears.

Stricture of the Ureter. This subject has been receiving increasing attention from urologists since the work of Hunner, of Baltimore, appeared. He has recently claimed that it is the cause of many unexplained hematurias and that by dilatation of the stricture the bleeding is stopped. Increased intracapsular tension, due to

pyelectasis or focal nephritis (tonsillar), may be responsible for the bleeding.

An example of this was a woman, aged thirty-two years, seen with Dr. E. Katz. For six months she had attacks of right renal colic accompanied by hematuria. There were also leukocytes in the urine. Roentgen-ray examination showed normal size, shape and position of the kidneys, and no evidence of a calculus. The first cystoscopy showed normal bladder and ureteral orifices. The

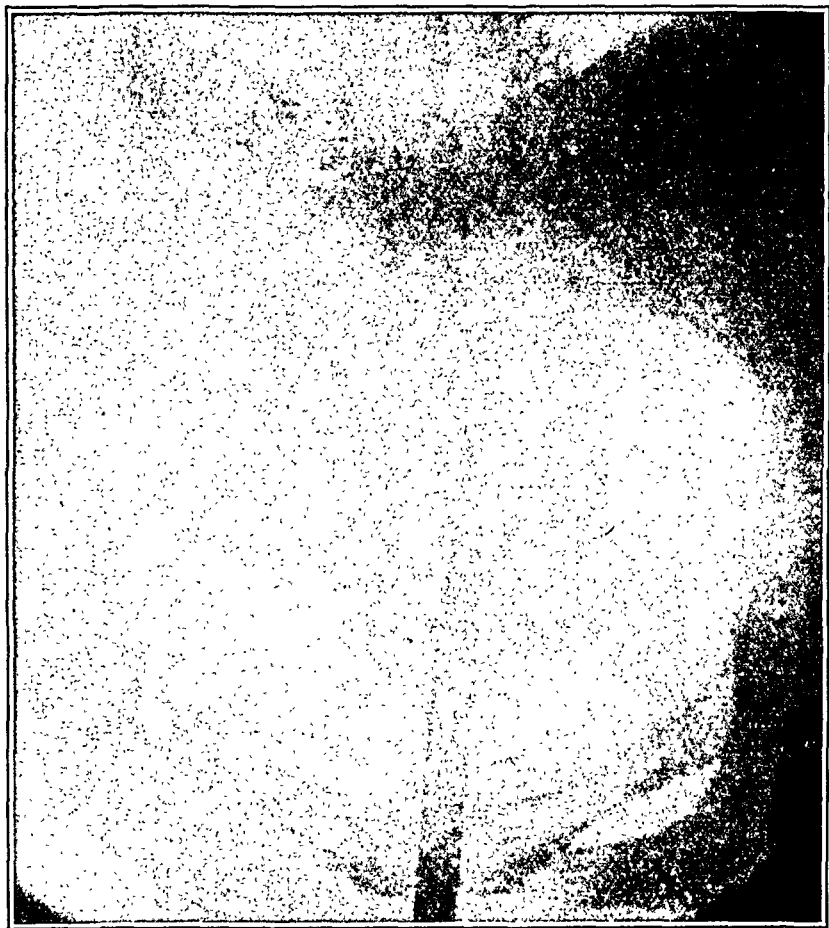


FIG. 1.—Bilateral ureterogram, showing dilatation above stricture of lower left ureter. Pain was contralateral.

right ureter was easily catheterized to the pelvis and a clear specimen obtained. The left ureter presented an impassable obstruction at 3 cm. and no flow could be obtained. The examination was repeated a week later and a No. 5 catheter could be passed 5 cm. only, but a profuse flow of urine containing blood cells and leukocytes was obtained. The function on this side was half that of the right, as determined by urea content and indigo-carmin excretion. A wax-tipped bougie passed against the face of the obstruction yielded no scratch mark. A ureteral pyelogram showed

dilated ureter, pelvis and calyces above the obstruction. Another examination was made, outlining both sides for comparison (Fig. 1). The stricture was then gradually dilated with wax bulbs and catheters up to No. 11 (Garceau catheter). All pain ceased, the urine cleared up completely. About four months later reëxamination showed a complete restoration of the left kidney and ureter to normal form and function. The patient has been well ever since.

Ureteritis and Pyelitis Cystica. Cystitis cystica is a rather uncommon disease, but well recognized by the urologist. The etiology is unknown, but it appears to be of inflammatory origin



FIG. 2.—Cross-section of ureter; autopsy specimen. Ureteritis cystica. Note tendency of mucosa to form papillomatous excrescences.

and is characterized by the presence of small cystic lesions of the mucosa, which on section are found to be inclusion cysts of the lining epithelium. Aschoff, Saltykow, Stoerck and Zuckerkandl have given excellent descriptions of the gross and microscopical pathology. The lesions may occur in any part of the bladder, but are most often seen on the trigone, about the vesical neck and the ureteral orifices. Similar lesions may be present in the mucosa of the ureters (Fig. 2) and renal pelves, and may be unilateral or bilateral. Perhaps it is the end-result of a preceding inflammatory or degenerative process.

In the ureter and pelvis it may cause obstructing masses, and there is a tendency to papilloma formation in addition. Hema-

turia from one or both sides may occur, due to secondary infection and ulceration. But there is often an associated nephritis (Fig. 3), which may in itself be responsible for the supravescical hematuria in some cases. The cystoscopic bladder picture is very characteristic, the lesions being commonly described as having a fish-eye appearance. The tropical disease of bilharzia must, however, be carefully excluded by examination of the urine for the ova of that parasite.

Four cases of this disease with associated supravescical hematuria have been observed: For example, a man, aged fifty years, was

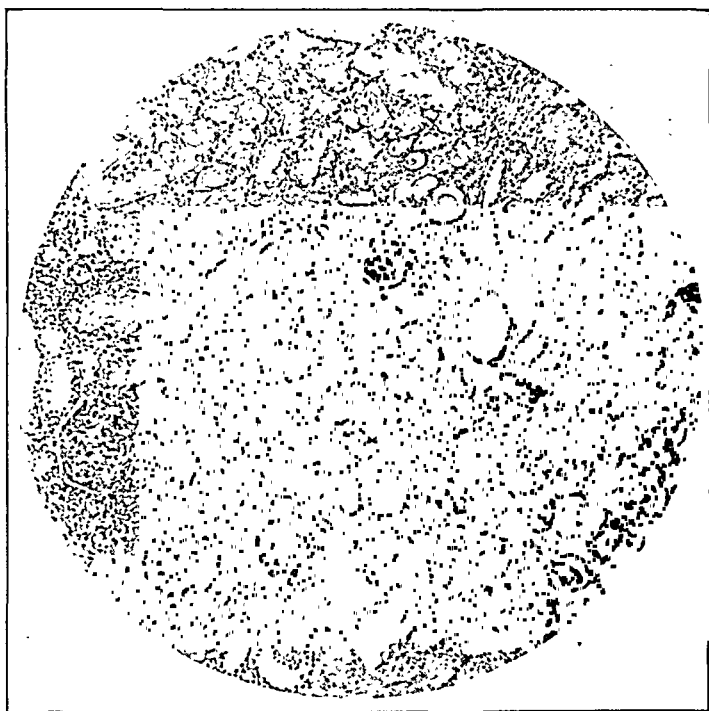


FIG. 3.—Focal nephritis in case of ureteritis and pyelitis cystica with hematuria.

admitted to the hospital, in 1919, with a history of intermittent hematuria for a year, and frequency of urination. Large areas of cystitis cystica lesions surrounded both meati and bloody urine issued from the left. The kidneys showed marked functional impairment. In 1921 he reappeared at my clinic, having been free of hematuria in the interval. The bladder showed the same lesions, but this time the blood was coming from the right ureter. Lavage of the renal pelvis with 1 per cent silver nitrate solution was followed by a cessation of bleeding.

Another patient with cystitis cystica and left-sided hematuria ceased to bleed after pyelographical examination, and a year later reported free of bleeding; but she had developed a condition of scleroderma involving the hands, feet and head.

Hydronephrosis. Without stones, and due either to congenital causes or obstructive conditions in the ureter, such as angulations, kinks and strictures, this condition may be complicated by hematuria. Such bleeding may result from rupture of varices in the pelvic wall, or from an associated papillitis or nephritis. The diagnosis of this condition is readily made by cystoscopy and pyelography, but a hydronephrosis may mask a tumor of the pelvis.

Primary Tumors of the Renal Pelvis and Ureter. This is a group of cases of great importance because of difficulties attendant upon making a correct diagnosis and because of the necessity of instituting proper surgical therapy. About 150 cases of this group have been reported in the literature, and in very few has the diagnosis been made and the proper therapy instituted.

The tumors fall into three classes: Papillomas, papillary carcinomas and solid carcinomas. The papillary growths are very apt to be multiple and tend to implant themselves along the ureter and in the bladder. In some cases a diffuse papillomatosis, involving both kidneys, both ureters and the bladder, exists.

The cases present a great variety of symptoms, and may readily be confused with some of the conditions already described. The presenting features are: (1) Hematuria; (2) pain due to renal colic, chronic distention of the kidney pelvis or extension of the growth; (3) enlargement of the kidney.

For practical reasons they may be divided into two groups:

1. Cases with visible tumor.
2. Cases with no visible tumor.

Cases with Visible Tumors. A papillary tumor may be seen in the trigonal or paratrigoal area, or fine finger-like projections may form a corolla about the ureteral orifice. A pedunculated tumor may protrude from the orifice constantly or only with the efflux of urine.

If cystoscopy is done in an interval free from bleeding one is likely to attribute the bleeding to the visible growth.

If the examination is made during a period of bleeding one may be surprised to find the blood coming not from the visible tumor but with the ureteral efflux.

For example, a man, aged fifty years, with hematuria had been cystoscoped and a small papilloma near the neck of the bladder had been destroyed by fulguration. The bleeding, however, had continued. I cystoscoped him subsequently and found a bloody efflux from the left ureter. A diagnosis of papilloma of the renal pelvis was made and removal of the kidney and ureter advised. Unfortunately the patient had a cerebral accident a few days later and died. At autopsy the left kidney was found enlarged, and the upper half of the pelvis was covered with a diffuse papillomatous growth of benign character.

Cases with No Visible Tumor. These naturally offer greater difficulties in diagnosis.

A man, aged sixty-one years, a patient of Dr. Beer's, had hematuria for one year. There was a large tender right kidney. When cystoscoped in a free interval a rather large adenoma of the prostate was found. The left kidney gave normal findings. In the right ureter an impassable obstruction at 8 cm. was encountered. Roentgen-ray showed no calculus. A wax-tipped bougie gave no scratch marks. Manipulation of the catheter against the obstruction produced brisk bleeding. A subsequent examination during a period of bleeding showed a bloody efflux from the right ureter. A diagnosis of primary tumor of the ureter was made, and at operation a large hydronephrosis and hydroureter were removed. At the lower end of the ureter was a benign papilloma about an inch in diameter.

The following case illustrates how difficult it may be to discover the true cause of renal hematuria and how many confusing factors may exist in a given case. A man, aged sixty-two years, was found to be bleeding from the left kidney. The phenolsulphonephthalein excretion was 18 per cent, and the blood chemistry showed some nitrogen retention; urea nitrogen, 40; incoagulable nitrogen, 96; uric acid, 4.8; creatinin, 3.6. Pyelogram of the left kidney showed a somewhat dilated pelvis with blunted calyces. The function of this kidney was much impaired, as determined by indigo-carmin excretion. At operation a small kidney with scarred surface was found; nothing could be felt in the pelvis. The peritoneum was opened and the opposite kidney was palpated and found to be likewise contracted. The organ was, therefore, simply decapsulated and a section removed for examination. The specimen showed an advanced interstitial inflammation with destruction of tubules and atrophy of glomeruli (Fig. 4). It seemed reasonable to believe that we were dealing with a hematuria due to nephritis.

Although no further gross bleeding occurred, red blood cells continued to appear in the urine. The patient's general health remained good. About a year later an attack of hematuria brought the patient to the hospital again. On cystoscopy, I found a small papilloma protruding from the left ureteral orifice, and suspected that this was an implantation from a growth in the renal pelvis which had been overlooked at the first operation. Pyelography showed a dilated and deformed pelvis (Fig. 5). The kidney and ureter were removed by Dr. Hyman and a papillary carcinoma filling the pelvis and invading the parenchyma was found (Fig. 6).

Tumors of the Renal Parenchyma. In 50 to 70 per cent of carcinomas, sarcomas and hypernephromas of the kidney parenchyma hematuria is the first symptom. Such bleeding often lasts but a few

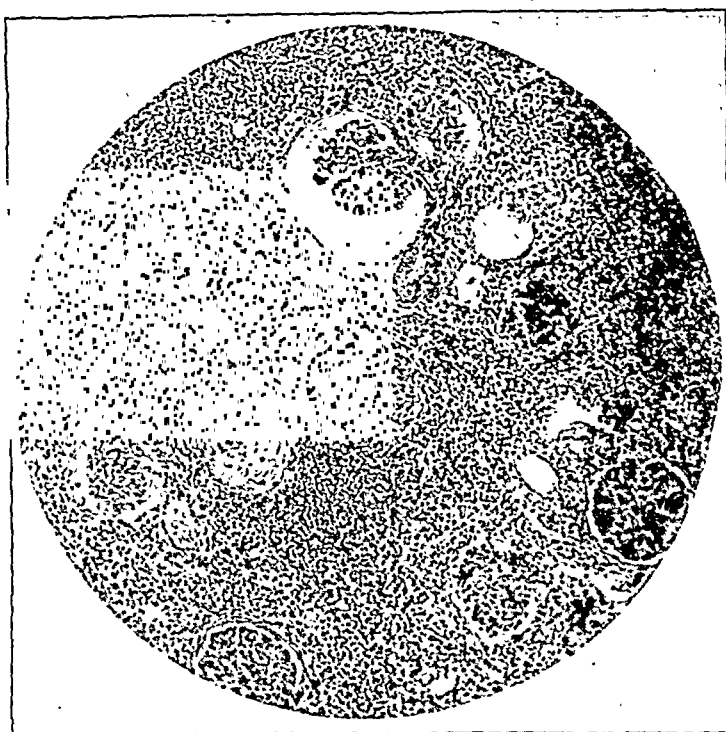


FIG. 4.—Specimen removed from bleeding kidney, advanced interstitial nephritis. Later proved to have tumor of renal pelvis.

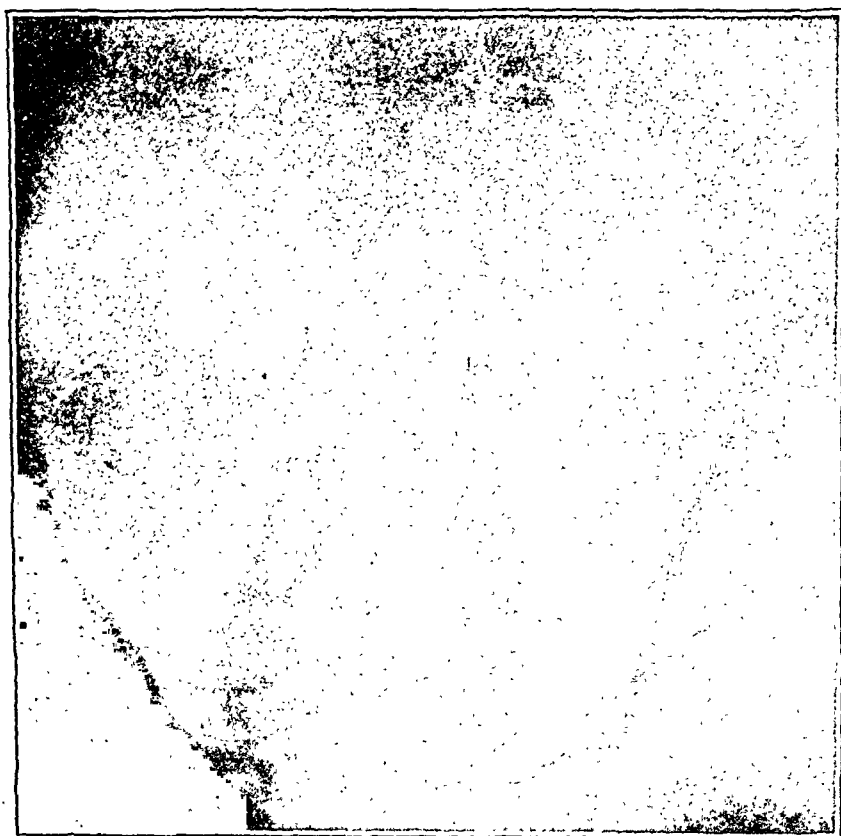


FIG. 5.—Pyclogram; tumor of renal pelvis.

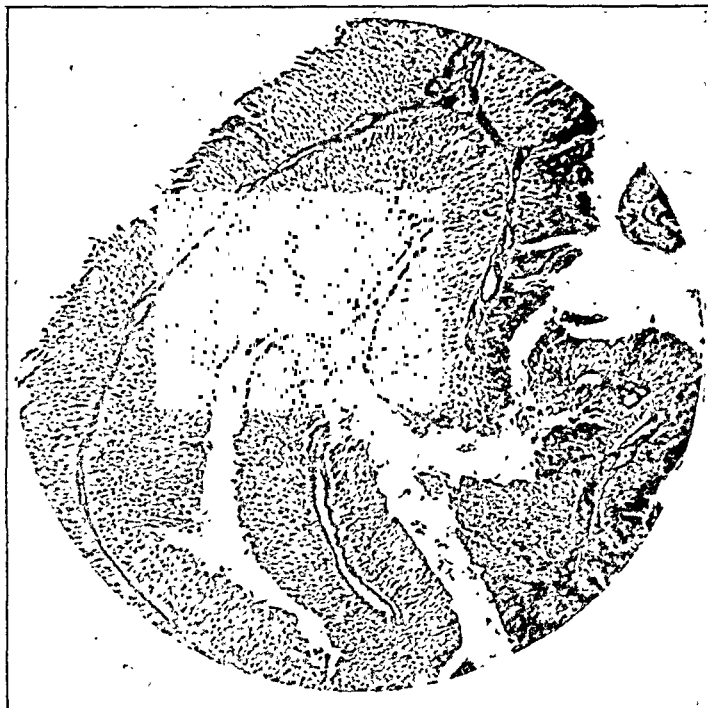


FIG. 6.—Microscopical section; papillary carcinoma of renal pelvis.

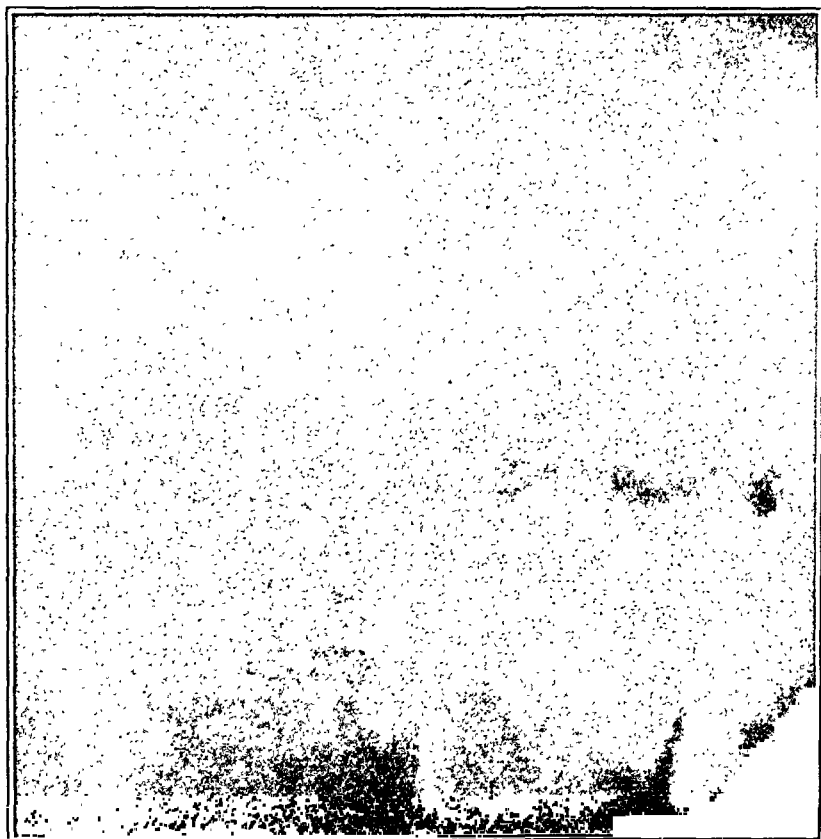


FIG. 7.—Pyelogram; papillary adenocarcinoma of lower pole of kidney; proven at nephrectomy.

days and may not recur for a long time. The spontaneous cessation of hemorrhage is an unfortunate occurrence because it frequently leads patient and doctor to minimize its importance. In no group of patients, therefore, is a prompt urological examination of so much importance. The tumors of the renal pelvis and ureter are likely to bleed more frequently and constantly, but the growths of the parenchyma may not manifest themselves again for a year



FIG. 8.—Pyelogram; papillary adenocarcinoma invading renal pelvis, proven at nephrectomy.

or more. In the meantime they have steadily progressed in size and have extended into the perinephritic tissues and renal vein, and when recognized have passed into an advanced and hopeless stage.

It is possible that the first bleeding occurs from dilated venules in the pelvis or uninvolved kidney tissue before the growth has actually invaded the pelvis. The pyelogram is probably the most valuable diagnostic agent in these cases, and shows a variety of deformations, displacements and filling defects (Figs. 7 and 8).

In some cases nothing can be injected into the pelvis because it is filled with blood or tumor tissue or compressed by the growth.* The induction or aggravation of bleeding by manipulating the ureter catheter in the pelvis is also of value. Occasionally tumor tissue or cells may be recovered by washing of the pelvis. The wax-tipped catheter or bougie helps exclude calculus. Functional tests will show impairment of the affected organ as compared with the healthy one. The presence of casts in the urine caused one man with hematuria to be treated for nephritis a whole year before he came to the hospital for urological examination. The bleeding was unilateral, the pyelogram showed marked deformation of the pelvis and at operation a hypernephroma of the kidney was found.

Thus far we have dealt with hematuria in which a well-defined pathology exists, although in the cases of stricture of the ureter, and of hydronephrosis the explanation of bleeding from the kidney is not so evident as in the other groups.

There are additional cases of renal hematuria which have been variously designated by writers as essential hematuria, symptomless hematuria, renal hemophilia, angioneurosis of the kidney, or "nephralgie hematurique." Rovsing spoke of mysterious renal hemorrhage and Klemperer of hematuria of the healthy kidney. These names indicate sufficiently the uncertainty as to the nature of these cases. The whole subject hinges upon this question: Should one conceive of hemorrhage from a normal kidney? Persistent efforts have been made by urologists to find a rational explanation for these cases. The result has been a progressive diminution in the number of unexplained hematurias and an increasing finesse in the study of the pathology of the affected organ. Certain difficulties present themselves, however.

1. The examination of a wedge of kidney tissue removed at operation has little value because: (a) If the tissue shows no lesion we cannot conclude that the entire organ is normal; (b) if the tissue shows an inflammatory or degenerative process we cannot conclude that this causes the bleeding. Most kidneys showing definite nephritis never bleed.

2. The examination of the whole organ removed at operation would seem to be sufficient but: (a) The urologist has learned that decapsulation or nephrotomy can cure these cases (as a rule, only those kidneys are removed in which the conservative operation has failed, and under such circumstances the primary condition is complicated by changes incident upon the first operation); (b) granted that the kidney is removed at the primary operation through error or because of the intensity of the bleeding, we cannot disregard the fact that the circulatory relations of the organ

* The use of perinephritic injection of oxygen or carbon dioxide (Carelli) may prove of assistance in demonstrating tumors of the kidney.

are disturbed in the process of its removal. Either artefacts are produced or a true vascular lesion is rendered undiscernible.

The following anatomical and pathological changes have been observed in cases of this group either on the operating table, in sections removed for study or in kidneys extirpated for hemorrhage.

1. Displacement of the kidney.
2. Abnormal mobility.
3. Perinephritis.
4. Slight hydronephrosis (pyelectasis).
5. Angioma or varix of renal papilla.
6. Incrustation of renal papilla.
7. Papillitis.
8. Bilateral nephritis with unilateral hematuria or alternating hematuria.
9. Unilateral nephritis (focal infections).

Israel, who concluded from his 14 cases that an anatomical or pathological basis always exists in renal hematuria points out that the apparent insignificance of the lesions described has caused skepticism as to their role in the production of the pronounced clinical symptoms. But, he observes, this disproportion between lesion and symptom is no more remarkable than that gross lesions can exist without producing any clinical signs.

Proof of the etiological relationship of the various lesions is offered by the results of therapy and of prolonged clinical observation.

Cases of hematuria in which nothing but abnormal motility could be demonstrated have been cured by nephropexy and some by a proper support. Cases of displacement, rotation and of fixation by adhesive perinephritis have been cured by decapsulation and nephropexy. The cause of the bleeding in these two types is a passive hyperemia or congestion due to interference with the venous return from the kidney. Moreover, it is believed by some authors (Newman, Randall, Schwyzer, Munk) that prolonged passive congestion leads to a patchy form of nephritis.

Perinephritis is to be regarded as evidence of a previous or quiescent inflammatory process.

Angioma or varix of a renal papilla was first described by Fenwick as an explanation of some cases. Cures have been effected either by resection of the papilla or by nephrotomy of the corresponding area deep enough to sever the vascular arches at the base of the pyramids. Several urologists have confirmed Fenwick's work (Pilcher, Cabot, Newman).

Incrustation of a papilla and inflammation of papillæ of the kidney have been demonstrated both macroscopically and microscopically.

Pyelectasis (mild hydronephrosis) may be present as the result of ureteral kinks in abnormally movable and displaced kidneys.

One must carefully examine for ureteral stricture in these cases. The bleeding in these instances and undoubtedly in some cases of obstructing ureteral calculus (Schwyzer) comes from the parenchyma. The improvement in drainage by ureteral dilatation, or nephropexy, and the diminution of intracapsular tension by decapsulation have resulted in cures.

The difficulties in establishing nephritis as the cause of unilateral hematuria by pathological methods have already been indicated. We have seen, however, that bilateral renal bleeding may occur in subacute hemorrhagic nephritis and in focal infectious nephritis. It is surprising that Fenwick had not observed such cases, and that Braasch thought bleeding in bilateral chronic nephritis was a terminal symptom. Israel was convinced, moreover, that unilateral hematuria occurs in cases of bilateral nephritis. This was proven by the later development of edema, cylindruria and uremia. Some of these cases were confirmed by autopsy. Many urologists and surgeons have concurred in Israel's opinion.

Payne and MacNider have studied the papillæ and the cortico-medullary zone of three bleeding kidneys which were removed. They found practically no lesions in the cortex, but there was an inflammatory fibrosis of the papillæ and cortico-medullary zones, with consequent obstruction to the venous return from the medulla and papillæ. Dilated veins in the pyramids and on the free surface of the papillæ were demonstrated as the source of the bleeding. These authors believe that an infection localized to foci in the medulla results in a fibrotic process of repair which in turn produces stasis, varicosities and hematuria.

Several cases are on record, however, notably those of Quinby, Koll and Stevens in which the kidney was removed at operation and in which careful histological study showed nothing but engorgement of the vessels between the straight collecting tubules and dilated vessels in the papillæ and beneath the pelvic epithelium. In some instances there were evidences of an inflammatory cellular and serous exudation. Two kidneys were removed at Mt. Sinai Hospital in 1914. Careful examination by the pathologist, Dr. Mandlebaum, failed to establish the cause of the bleeding.

The success of nephrotomy performed in these obscure cases of unilateral hematuria either for purposes of exploration or with a view to cure has been explained in various ways. Pilcher believed that the nephrotomy divides six main collecting veins and permanently closes them by thrombosis. Spitzer believes it is effectual only because the sutures passed to control the hemorrhage cause a partial nephrectomy.

The following cases are examples of the conditions discussed:

Case Reports, CASE I.—A traffic officer, aged forty-one years, complained of hematuria for four weeks. There were no other

urinary symptoms. Six months prior to this he had a severe cold and cough, lasting six weeks. The lower pole of the left kidney was palpable. The blood was seen coming from the left ureter. All examinations proved negative. The pyelogram showed a normal outline, but the kidney was ptosed. At operation a bulging was found on the anterior aspect near the hilum, but nephrotomy showed no gross change. The kidney was then decapsulated. The tissue excised showed marked congestion, especially of the glomeruli and a parenchymatous degeneration (Fig. 9). He has been well ever since (three years).

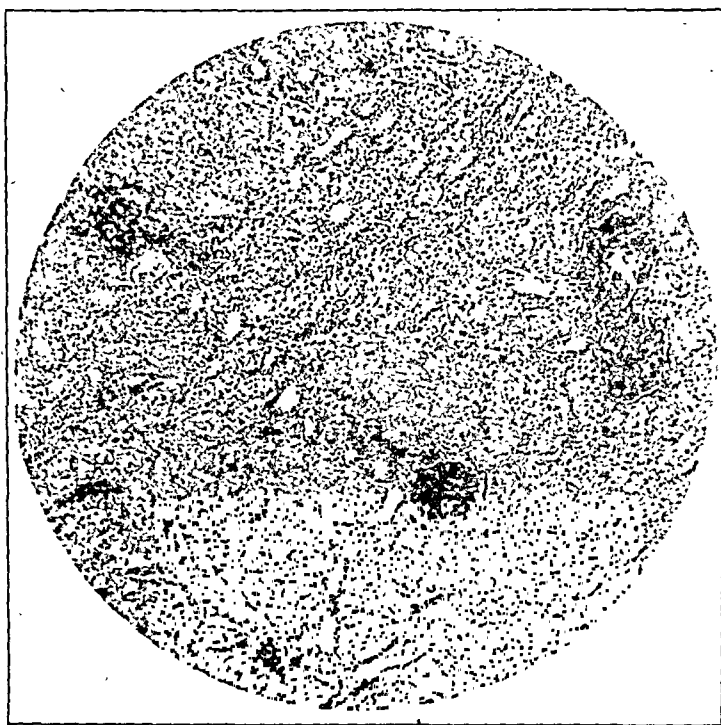


FIG. 9.—Section of renal parenchyma removed at operation in case of unilateral hematuria; congestion and parenchymatous degeneration.

CASE II.—A conductor, aged forty years, complained of hematuria for six weeks with no other symptoms. He presented a marked scoliosis to the right. The blood was coming from the left kidney. There was no disturbance in function. The kidneys appeared normal in size and shape, but were definitely displaced due to the scoliosis. Pyelogram showed no abnormality. At operation a definite perinephritis was found and depressed scars. Excised tissue showed marked congestion and areas of focal nephritis. He has remained well two years after the decapsulation of the kidney.

CASE III.—A woman, aged thirty-six years, had two recent attacks of hematuria coming on after chills and fever. There was right lumbar pain radiating to the genitals. There was no difference in function between the two kidneys, but the bleeding was found to come from the right side. A pyelogram showed a dilated pelvis and calyces poorly outlined. At operation the ureter was found so thickened as to suggest tuberculosis and the kidney was removed. The specimen showed a peculiar exudative inflammation involving all the papillæ (Fig. 10), and a dilated pelvis; no other lesion.

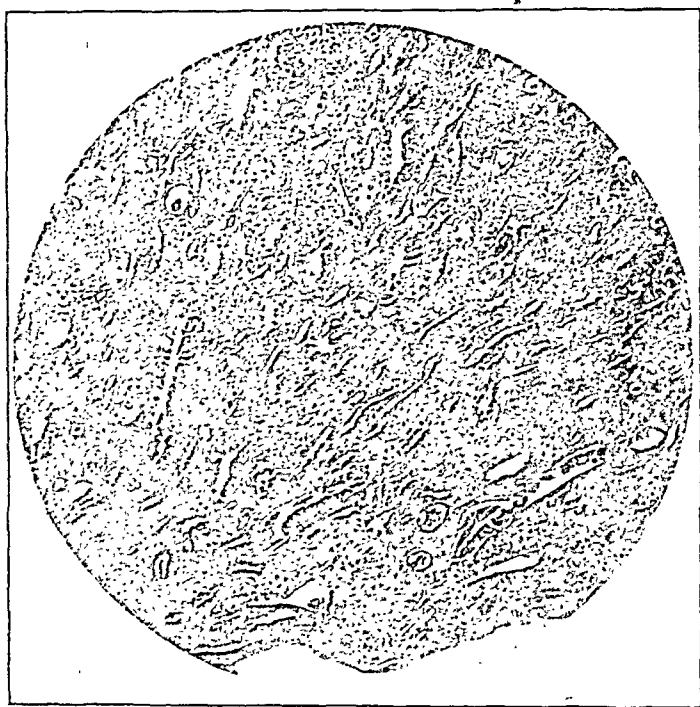


FIG. 10.—Section of papilla in case of hematuria due to papillitis with fibrosis. Cortex showed no abnormal changes.

CASE IV.—A woman, aged fifty years, had suffered with malaria for several years. For the past ten months she had intermittent attacks of hematuria with a dull ache in the left flank. The total phenolsulphonaphthalein elimination was 26 per cent. The left kidney function was about half that of the right. Albumin was present in both ureteral specimens and blood in the left. Pyelogram showed a dilated pelvis, and the middle calyces not well filled. The kidneys appeared small in the roentgen-ray. At operation nothing abnormal was found except a small and somewhat contracted kidney. Nephrotomy was negative. The excised tissue showed focal nephrosclerosis. Following decapsulation and nephrotomy she remained well for several months, when hematuria occurred as vigorously as before. Dr. Beer cystoscoped the patient

and found the blood coming from the unoperated kidney (right). Here then is a definite case of bilateral focal nephrosclerosis bleeding first from one kidney and subsequently from the other.

Management of Supravesical Hematuria. Every case of hematuria should be regarded as due to neoplasm until proven otherwise. This implies an exhaustive diagnostic study of the case, using all known methods of examination.

Unilateral Hematurias. In cases of unilateral hematuria *in which all examinations have proved negative* cessation of bleeding has been effected for considerable time or permanently by various modes of treatment. Young and Kretschmer applied epinephrine through the ureteral catheter, Rytina used nitrate of silver and Barringer serum. Levy noted that distention of the pelvis in the process of pyelography frequently caused a cessation of bleeding. But no patient treated in this way should be permitted to pass out of observation, and it must be carefully explained that a recurrence of bleeding necessitates immediate reexamination.

Cases in which pyelography shows a dilatation of the pelvis and calyces had best be suspected of neoplasm of the renal pelvis unless some other good reason can be established, such as calculus or ureteral stricture or ureteral angulation. If the pyelectasis is due to abnormal mobility and ureteral angulation a kidney support may be sufficient. If stricture has been demonstrated progressive dilatation is indicated.

In all cases with negative findings in which the simpler measures fail or in which bleeding recurs, and in all cases of unexplainable pyelectasis, nothing short of a thorough exploratory nephrotomy with inspection of the renal pelvis will meet the indications.

Decapsulation and wide nephrotomy has given good results in hematurias of nephritic origin. Varices of the papillæ may be treated similarly, but have also been cured by cauterization and papillectomy.

In tumors of the ureter and renal pelvis the operation of complete aseptic nephro-ureterectomy, as described by Beer, should be employed. Other renal tumors require nephrectomy.

The well-known principles of urological and surgical treatment are applicable to the cases of calculus and tuberculosis. Not infrequently an unsuspected calculus has been found when exploratory nephrotomy has been resorted to. A thickened ureter and increase of peripelvic fat should suggest tuberculosis to the operator.

The hematurias due to pyelitis and ureteritis cystica may be controlled by silver nitrate lavage of the pelvis and ureter. In some cases decapsulation and nephrotomy may be necessary.

Bilateral nephritic hematurias may yield to medical and dietetic treatment or to the removal of foci of infection. Bilateral decapsulation may be required in persistent cases.*

* I wish to acknowledge my indebtedness to Dr. Beer for the privilege of using the material from his service, and to thank Dr. Jaehes for the roentgen-ray

BIBLIOGRAPHY.

1. Aschner: Clinical Importance of Aseptic Infarction of the Kidney, AM. JOUR. MED. SCI., 1922, 164, 386.
2. Aschner: Primary Tumors of the Ureter, Surg., Gynec. and Obst., 1922, 34, 749.
3. Beer: Aseptic Nephro-ureterectomy, Jour. Am. Med. Assn., 1921, 77, 1176.
4. Braasch: Clinical Observations on Essential Hematuria, Jour. Am. Med. Assn., 1913, 61, 936.
5. Buerger: Concerning Certain Types of Hemorrhagic Nephritis, Med. Rec., 1918, 94, 1057.
6. Cabot: Varix of Papilla of the Kidney, AM. JOUR. MED. SCI., 1909, 137, 98.
7. Fenwick: Symptomless *versus* Painless Hematuria, Handbook of Cystoscopy, 1904, p. 380.
8. Fowler and Waterman: Essential Unilateral Hematuria, Internat. Abst. Surg., 1922, 34, 441.
9. Haynes: Unilateral Hematuria Due to Pyelitis Cystica, Am. Surg., 1908, 48, 417.
10. Israel: Chir. klin. der Nierenkrankheiten, 1901, Chapter xiii.
11. Koll: Undiagnosed Renal Hemorrhage, Jour. Urol., 1922, 8, 115.
12. Levy: Essential Hematuria, Surg., Gynec. and Obst., 1922, 34, 22.
13. Newman: Renal Varix and Hyperemia, Brit. Jour. Surg., 1913, 1, 4.
14. O'Neil: Hematuria of Chronic Infectious Focal Nephritis, Internat. Jour. Surg., 1920, 33, 72.
15. Payne and MacNider: Unilateral Symptomless Hematuria, Jour. Am. Med. Assn., 1916, 67, 918.
16. Pilcher: Renal Varix, Ann. Surg., 1909, 49, 652; Surg., Gynec. and Obst., 1912, 15, 59.
17. Quinby: Renal Pelvis in Two Cases of Essential Hematuria, Jour. Urol., 1920, 4, 209.
18. Randall: Jour. Am. Med. Assn., 1913, 60, 10.
19. Seelig: Hematuria in Appendicitis, Ann. Surg., 1908, 48, 388.
20. Schwyzer: Essential Hematuria, Ann. Surg., 1909, 49, 628.
21. Spitzer: Jour. Am. Med. Assn., 1914, 63, 2110.
22. Stevens: Hematurias of Obscure Origin, Jour. Am. Med. Assn., 1922, 79, 1302.
23. Young, E. L.: Prenephritic Renal Hematuria, Surg., Gynec. and Obst., 1920, 31, 418.
24. Young, H. H.: Jour. Am. Med. Assn., 1907, 47, 1654.

UNCOMPLICATED DISLOCATIONS OF THE SHOULDER: THEIR RATIONAL TREATMENT AND LATE RESULTS.

BY KARL SCHLAEPFER, M.D.,

NEW HAVEN, CONN.

Introduction. Dislocations of the shoulder occur so frequently in the hurried life of today that the experience of a large hospital such as the surgical clinic at Zürich, Switzerland, during the last twenty years, 1899-1919, might prove helpful in bringing forth valuable suggestions with regard to the most rational treatment of these everyday accidents. From the follow-up survey of these cases, we may draw some conclusions as to the best form of therapy.

Two factors govern the treatment of any dislocation: The immobilization of the limb after proper reduction, permitting a healing of the tears in the joint capsule and resorption of the blood extravasated into the joint cavity and into the surrounding soft tissue. The second factor which combats the resulting muscular atrophy is active and passive motion to keep up the tone in the muscles, thus preventing adhesions within the joint and contractures. This second factor is partly opposed to the first one, but becomes more and more important in securing a complete restitution of function within a minimal time. The relative merit of these two factors is still a matter of controversy in the treatment of fractures and dislocations. Our survey might again arouse interest in a special group: the uncomplicated dislocation of the shoulder. Cases with complications were included in our essay insofar as the usual treatment was not interfered with.

A. GENERAL REMARKS. Shoulder dislocations are the most frequent (51 to 52 per cent: Finckh) of all luxations. This is due to the marked exposure of the shoulder joint and the small articulating surface for the humerus in the shallow glenoid fossa of the scapula, necessitating its reinforcement by accessory ligaments.

This lesion occurs the most frequently in middle age: children are very seldom affected, as seen in the accompanying chart:

Age, years.	Bruns-Finckh.	Schlaepfer.	Krönlein.
0 to 10 . . .	1	0	0
11 to 20 . . .	2	10	2
21 to 30 . . .	15	15	55
31 to 40 . . .	28	16	45
41 to 50 . . .	51	24	48
51 to 60 . . .	71	21	36
61 to 70 . . .	46	22	19
71 to 80 . . .	9	12	2
	<div style="display: flex; justify-content: space-around; align-items: center;"> 79 per cent 66.6 per cent 50.7 per cent </div>		
Total . . .	223	120	207

The predominance of males is explained by their greater exposure to injuries in occupation, although modern traffic increases the liability to accidents of both sexes.

In our series 71 (59.1 per cent) dislocations occurred on the right side, 49 (40.8 per cent) on the left. Finckh reported 67 per cent on the right side; Körteweg in a large series found about the same frequency of occurrence on each side; Krönlein had 56 per cent left-sided lesions.

B. FORMS OF DISLOCATIONS. We usually distinguish between an anterior and a posterior dislocation from the respective position of the head of the humerus to the glenoid fossa of the scapula. Of our 120 cases of shoulder dislocations 113 (94 per cent) were anterior; only 7 (6 per cent) belonged to the posterior form (subspinous dis-

location). Finckh from Bruns clinic quoted among 206 luxations, 201 (92.5 per cent) anterior and 5 (2.4 per cent) posterior.

The most frequent anterior dislocation is the *subcoracoid form*, resulting from a direct pressure injury to the head of the humerus. In some cases the arm is held in hyperabduction, the greater tubercle fixed against the upper glenoid border, the surgical neck against the acromion, the head is driven through a weak place of the capsule on the anterior lower aspect. Partly by gravity, partly by muscular action the arm falls down and the head finally rests underneath the coracoid process. In exceptional cases with extensive laceration of capsule and muscle a *subclavicular form* will result. When the head becomes fixed underneath the glenoidal border we speak of a *subglenoidal* (axillary) dislocation. With the arm fixed in an elevated position, we are confronted with the *erect luxation*. In a few cases the head is driven within or underneath the subscapular muscle, thereby touching the preglenoid aspect of the scapula: *pre-scapular luxation*.

The posterior dislocation is very rare, the head being situated either below the acromion, the so-called *subacromial form*, or underneath the scapular spine as a *subspinous dislocation*, between the teres minor and infraspinatus muscles.

1. **Subcoracoid Dislocation.** *Frequency.* Of the 113 anterior, 108 (90 per cent) are subcoracoid and 5 (4 per cent) axillary. Gubler's recent statistics quote 111 (80 per cent) subcoracoid out of 143 cases. Da Costa mentions 75 per cent as the average for this most frequent form. Variation in the relative frequency of the different forms are due to the rules of admission governing the hospital. In a compilation including also straight ambulatory cases, omitted in our series, we obtain figures slightly different from the above.

Sex. Of our 108 *subcoracoid dislocations*, 100 occurred in males, thus demonstrating that a great number of these luxations resulted from an accident during work. The 14 (13 per cent) drunkards belong to a special group of misguided seekers of happiness. In 62 cases the right side was affected (57 per cent), in 46 the left. Gubler found 48 (43.2 per cent) on the right side and 63 (52.8 per cent) on the left. We see that the incidence of dislocations does not vary greatly on the two sides of the body.

Age, years.		
0 to 10	0
11 to 20	10
21 to 30	14
31 to 40	13
41 to 50	22
51 to 60	21
Over 60	28
Total	108

71 (66 per cent)
(61 to 70: 16)

In children dislocation is rather unusual. Epiphysiolysis or a fracture of the neck is more frequent. Sixty-six per cent of our cases occurred in persons over the age of forty.

Etiology. Falling on the shoulder and dislocation by direct action was responsible in the majority of our cases. This was probably the causative factor also in the 14 drunkards. In 4 cases the blow was directed from above or behind. In 5 instances the patient tried to mitigate the fall with his hand or elbow. In 1 case a sudden violent muscular action was responsible for the dislocation. In 1, a vigorous young soldier of twenty years, the dislocation occurred while throwing a camping blanket weighing 2 kilos over his shoulder. In another observation a workman, aged twenty-nine years, was lifting a heavy load of 200 kilos when he felt a sudden crack in his shoulder. Undoubtedly an abnormal condition of the capsule created a predisposition. Kaufmann quotes a subcoracoid dislocation caused by muscular action alone. Krönlein treated a woman with a dislocation acquired during an eclamptic attack. Jacquemin's patient was painting a ceiling. Baumann's patient touched an electric current with his hand, a tetanic contraction of the muscles of the shoulder girdle being responsible for the dislocation.

Diagnosis. In most of the cases the picture was a typical one, based on the changed outline of the shoulder (angulation below the acromion) and the flattening of the infraclavicular fossa. The relative fixation of the upper arm in a slightly abducted position was always characteristic. Thorough and thoughtful examination gave to the physician in almost all cases an understanding of the position of the head of the humerus, subsequently verified by roentgen-rays. The roentgen-rays have to exclude the presence of complicating fractures, not demonstrable on palpation. In cases with intensive swelling due to extreme extravasation into the soft tissues, the roentgen-rays are of the utmost value in explaining the special features of the case.

Complications. 1. *Nerve Injuries.* In a fifty-year-old drunkard a palsy of the hand, forearm and deltoid muscle was present. Anesthesia was noticed in the distribution of the ulnar nerve. No improvement was noticeable when the patient left the hospital after one month; further examination was impossible. In a second case with palsy in the distribution of the ulnar nerve, the sensory palsy subsided; but the motor disturbance persisted. Another case with complete radial (musculospiral) palsy involving also the circumflex (axillary) nerve showed a complete atrophy of the deltoid muscle after five years. The remaining muscles exhibited considerable weakness. In Gubler's compilation of 252 cases 10 (3.9 per cent) had a nerve palsy, involving generally several nerves, but clearing up gradually within a few months.

Lesions of the Bloodvessels. In most of the histories no note is made regarding the radial pulse on the two sides, although this is

a point of special importance before starting any manipulation. It should always be combined with investigation of the sensory condition of the skin, particularly in the hand. Slight changes are not often reported spontaneously by the patient. If recorded only after reduction patient may date it from the manipulations.

Fractures. In 8 (7.4 per cent) cases a *fracture of the greater tubercle* was found; in 7 instances it did not interfere with the healing. In the remaining one the loose fragment was removed by operation three days after the accident. Gubler had this complication in 7 per cent of his cases. Before the time of the roentgen-ray this complication was assumed to take place much more frequently, due to the fixing action of the supraspinatus muscle for the head of the humerus (Bardenheuer: 50 per cent). Since roentgen-rays are taken, preferably in two planes, a sagittal (antero-posterior) and a frontal (from the axilla: Iselin), this fracture is less frequently observed, mostly in older persons. Finckh had only 4 among 223 luxations. In our series of dislocations with delayed reduction we had 30 per cent, all among old people, thus justifying Bardenheuer's statistics.

Fracture of the surgical neck is mentioned in 2 cases out of 108. One was a boy, aged fourteen years, another a mail-carrier, aged fifty-one years. Gubler had 2 cases among his 252 dislocations, a male, aged sixty-five years, and a thirty-seven year old man with a temporary palsy of the circumflex and the musculospiral nerve. We had a young man, aged twenty years, with a *fracture of the acromial end of the clavicle*. Luxation of the acromial end of the clavicle, fracture of the neck of the scapula or of the coracoid process or a pertubercular fracture are complications not encountered in our case records.

Deaths. In older persons even a shoulder dislocation becomes a serious condition due to complications which may arise during the after-treatment. Three deaths occurred in this group: A man, aged seventy years, died from a pulmonary embolism three weeks after the accident, subsequent to a thrombosis of a vein of the calf. This demonstrates clearly the importance of daily active movements and massage of the lower limbs, in old persons confined to bed. A workman, aged seventy-three years, developed a lethal bronchopneumonia the day after the accident. This could possibly have been prevented by taking the patient out of bed for several hours every day or at least changing his position in bed frequently. In a housewife, aged eighty-two years, the shoulder dislocation was complicated by multiple rib fractures and fracture of the pelvis, with fatal fat embolism.

Treatment. A thorough clinical examination should precede any treatment, giving an accurate idea about the position of the head. The roentgen-rays form a truthful test and a guide for eventual complicating fractures. With Prof. Krönlein (1899 to 1911) the Schinzinger method was the method of choice for reduc-

tion in any uncomplicated case. The Kocher modification added elevation of the upper arm in a sagittal plane after its preliminary adduction to the trunk with subsequent outward rotation of the flexed forearm. This technique used formerly only in exceptional cases became in 1911, the routine procedure of Prof. Sauerbruch. Krönlein's habit was to reduce the arm without general anesthesia; a preliminary hypodermic injection of morphine, however, being usually given. Gentle manipulations were combined with an effort to divert the patient's attention from his condition. The majority of cases could be reduced successfully in this way. Kaufmann reports that out of 300 cases where he used the Kocher method in this way he had to resort to general anesthesia in only 1 per cent. In one of our observations, a subcoracoid dislocation, several attempts even under general anesthesia were fruitless. In a final trial more strength than proper was used. A sudden crack was heard. A fracture of the neck had resulted from too forcible manipulations, which are less liable to be utilized when reducing without the use of general anesthetic.

In seven instances a modified Mothe-method was applied (heel-in axilla method). Often a sudden pulling of the arm toward the contralateral pelvic brim (Riedel) proved to be successful. In 1 case a permanent extension on the dislocated humerus in a perpendicular axis, patient lying on the unaffected side did not relieve the malposition. This method (Hofmeister) is very efficacious in neglected cases, bringing about a gradual relaxation of the contracted shoulder muscles and thus rendering the difficult reduction possible.

After-treatment. From 1899 to 1911 with Prof. Krönlein the reduced arm was immobilized for one to two or three weeks in a sling (mitella). In exceptional cases the arm was fixed to the thorax by a Velpeau bandage. After this time daily massage with active and passive motion was started, increasing in degree every day. In the meantime the arm was kept in a sling for perhaps a week. With Prof. Sauerbruch the time of immobilization was shortened to a few days or at most a week. This was the technique generally accepted in all the large clinics of Europe, also by Küttner, whose results will be reviewed later.

Of our 108 cases 65 left the hospital within a few days and continued treatment in the dispensary. They all got well and did not require later readmission. Twenty left the hospital within thirty-two days with a normally movable shoulder-joint. Of the remaining 23 cases 8 were reexamined; 7 had a perfect function. 92 (85.2 per cent) of our cases recovered with a freely movable shoulder-joint. Two of those (aged fifty-six years and forty-four years) complained of radiating pains in the shoulder when the weather was changing.

Schmidt, who treated 27 cases along the same line had 22 (81.4 per cent) cured. In the other instances the lateral elevation was par-

ticularly restricted (5 cases or 18.6 per cent). Schulz from Küttner's clinic found that from 54 patients only 7 (13 per cent) had a normal function: In 22 per cent the result was satisfactory; a restriction in the elevation of the arm and a muscular weakness persisted. Twenty-four (48 per cent) could not elevate the arm over a horizontal plane. In 65 per cent of the cases the working capacity was diminished by 20 to 30 per cent; in 10 cases even to 50 per cent. In the analysis of these cases Küttner proposed early movement as a remedy for such mediocre results.

The time necessary for healing in our series was thirty to thirty-five days. We were not able to follow up all our cases as Gubler did, whose cases were taken from the Swiss accident insurance reports. He calculated from 184 uncomplicated cases of subcoracoid dislocation, an average duration for cure of thirty-eight days; *i. e.*, when patients could resume their previous occupation without any complaint. His accurate statistics show very well that the older the patient *the longer it takes to heal* (see accompanying table):

Age, years.	Duration.			
	One month.	Two months.	Three months.	More than 3 months.
0 to 20	20 (87.0 per cent)	2 (8.7 per cent)	1 (4.3 per cent)	
21 to 30	41 (87.2 per cent)	6 (12.8 per cent)		
31 to 40	19 (52.8 per cent)	17 (47.2 per cent)		
41 to 50	15 (41.7 per cent)	14 (38.0 per cent)	5 (14.0 per cent)	2 (5.5 per cent)
51 to 60	6 (30.0 per cent)	7 (35.0 per cent)	4 (20.0 per cent)	3 (15.0 per cent)
61 to 70	2 (12.5 per cent)	7 (43.7 per cent)	3 (18.8 per cent)	4 (25.0 per cent)
Over 70	4 (66.6 per cent)	1 (16.2 per cent)	1 (16.2 per cent)

Körteweg who made a similar survey of cases in Holland, as did Gubler in Switzerland had an average duration of fifty-five days. The difference is partly explained by the fact that Körteweg had more cases treated in the clinic and less straight ambulatory patients.

A revolution in the treatment of shoulder dislocation was brought about in 1911 by de Marbaix's *functional method*, whereby active and passive movements were instituted immediately after reduction. Mechano-therapy, he thinks, is not as important as these movements performed daily in a very extensive way from the beginning of the treatment. With an experience of 157 cases, de Marbaix never observed a relaxation. After eighteen days of this treatment 97 per cent of the patients could resume their previous occupation. The 3 remaining cases showed a chronic arthritis (peri-arthritis humero-scapularis). Even this amount of active treatment could not prevent this incurable condition, whose etiology is still the center of controversy and so very unsatisfactory for any treatment.

The compilation of de Marbaix illustrates very well the ill-effect of immobilization in uncomplicated cases of shoulder dislocation:

	Average time required for healing, days.	Cases.		Remarks.
		Total.	Cured.	
Sudden extensive active mobilization.	18	97	94 (97.9 per cent)	2 cases (40 per cent crippled). 7 cases (100 per cent invalid).
Mobilization after <i>one</i> week	55	11	11 (100.0 per cent)	
Mobilization after <i>two</i> weeks	121	5	3	
Mobilization after <i>third</i> week	300	7	0	

The movements maintain the tone of the muscles, and facilitate the blood flow within and between the muscles, thus shortening the time necessary for the resorption of extravasated blood. Within the joint less adhesion formation with subsequent arthritic changes is possible. Küttner in reviewing his bad functional results (see Schulz) made the statement that this might be improved by the inauguration of early active and passive movements. Patients who did not return to the clinic after reduction, but assumed their duties immediately, usually showed a perfect function, supporting in this way the principles of the treatment of de Marbaix. Thiem, Kaufmann, Körteweg and Gubler became strong advocates of de Marbaix's treatment. Although the statistics prove its superiority, this method is not yet generally accepted. It may be that it is too inconsidered of the natural human feelings that follow a serious injury, especially as the movements may be somewhat painful at the beginning. The principle has to be kept in mind; slight difficulties in the details of its application according to the type of person we are dealing with, should not lead to a complete rejection of such a valuable method. Möltgen added to this method distension of the shoulder-joint by Hackenbruch clamps, to diminish the pain. He shortened the time of healing in his series to fourteen days. This is another proof of the value of the functional therapy. As de Marbaix says, this therapy applies to every form of properly reduced uncomplicated shoulder dislocation. As the subcoracoid form is the most frequent, we have discussed the treatment in connection with this most frequent luxation.

2. **Axillary Dislocations.** Only 5 (4.3 per cent) cases belong to this group, thus proving the relative infrequency of this type of dislocation. All observations concerned males of twenty, thirty, forty, forty-four and sixty-six years of age. Twice the lesion was on the right side; three times on the left.

Gubler had among 31 (21.7 per cent), 20 on the left side and 11

on the right, with an average duration of healing of forty-three days. Twenty-nine (93.5 per cent) healed completely; 2 had a permanent defect.

Two cases belonged to the erect and horizontal type of dislocations. In 1 case the arm was fixed in an elevated position (erect luxation). The other, a sixty-six year-old farmer, had his arm fixed in an abducted position of 110° (horizontal luxation). In three other observations the force was probably directed from above.

Diagnosis. The diagnosis was made in our cases by examination and confirmed by roentgen-rays. A fracture of the greater tubercle in 1 case did not interfere in any way with the usual treatment.

Treatment and After-treatment. This was the same as that outlined for the subcoracoid type.

In no case was the reduction particularly difficult. Immobilization for the first week was always instituted. Then active and passive motion, increasing daily, followed or preceded by massage, helped to bring back the function.

Late Results. Three of these 5 cases were reexamined years after the accident. They were without any symptoms of impaired function. Two cases we lost track of.

3. Posterior (Subspinous) Luxation. In 7 cases observed, all were males. In all the *right* side was affected. Five were over sixty-five years of age, the other 2 about forty. In 6 out of the 7 cases a *direct* fall on the shoulder was the responsible injury; fall on the elbow was recorded in 1 patient's history.

Diagnosis. In 1 case the virtual lengthening of the upper arm was mentioned; another case seemed to have presented a shortening. In a view from the side, the axis of the humerus was directed backward with its upper end. In 1 case the arm almost touched the thorax; a relative fixation was mentioned in all except 1 record. Unfortunately the roentgen-rays of these cases were not at hand. We do not know the details of eventual complications. In an eighty-four-year-old farmer a fracture of the neck of the shoulder blade was present. This was the cause of the head of the humerus dislocating after every reduction. The patient was discharged unimproved after twenty-seven days. A woman, aged seventy-four years, had a simultaneous fracture of the posterior border of the glenoid fossa, leading to the same condition as in the preceding case. Movements were possible to a certain extent.

Death. A tailor, aged sixty-four years, died on the fourth day of double pneumonia.

Treatment. In these uncomplicated cases, reposition was effected as usual by the Kocher method without any difficulty, except in 1 case where seven unsuccessful attempts preceded the reduction. Thirty days was the average time patients were in the hospital. They were not completely cured on discharge. Changes of domicile unfortunately rendered a later examination of these cases impossible.

4. **Cases of Subcoracoid Dislocations of Delayed Reduction.** A valuable appendix to our paper is an investigation of the cases where the reduction of the subcoracoid luxation was postponed for a variable length of time. It demonstrates the importance of a thorough clinical diagnosis verified by roentgen-rays with adequate treatment and points out the complications resulting from neglect of these procedures. Of the 16 cases, 11 were male, and 5 females. Two were in the fourth decade, 5 in the sixth, 4 in the seventh and 3 in the eighth decade of life. In 5 (31 per cent) the greater tubercle was broken off, thus demonstrating the fixing action of the supraspinatus muscle for the head of the humerus. The extensive swelling setting in immediately after the injury was in these older people due to extravasation from sclerosed vessels, and the omission of roentgen-rays examination was responsible for these cases being treated as contusions of the shoulder for a variable length of time, until the persistent impairment of function urged another explanation than the reflex action of a painful contusion.

Few Days Delayed. In a carpenter, aged fifty-seven years, many maneuvers for reduction were made by different doctors in the first four days before he was sent to the hospital. After several fruitless trials the head jumped back into place by using the elevation-extension method. A concomitant fracture of the greater tubercle may have been a primary lesion or resulted from these manipulations. The final result obtained was functionally satisfactory.

A man, aged sixty-four years, was treated for contusion with compresses. After four days a roentgen-ray examination revealed the true nature of the injury. Reduction was easily performed. For two weeks the arm was bandaged to the thorax. Then passive motion was employed, the arm being in the meantime kept in a sling. No improvement being observed, a roentgenogram was taken, which showed a dislocated humerus with fracture of the surgical neck. An operation was rejected on account of the age of the patient, the chances for a functional improvement being too small. With greatly restricted mobility the patient left the hospital.

Three and a Half Weeks Delayed. A painter, aged fifty-one years, was treated for contusion during three and a half weeks, then he was referred to the hospital. After repeated fruitless attempts to reduce the subcoracoid dislocation an open reduction was performed. Ankylosis of the shoulder-joint resulted. Some motion with the scapula proved rather useful.

One Month Delayed. A smith, aged sixty-two years, fell on his shoulder. He continued to work for a day and a half; then he stopped on account of rheumatic pains. After a month he came to the hospital. Several attempts to reduce the dislocation proved unsuccessful. Finally it was reduced, and the arm kept immobile for sixteen days. Though prolonged active and passive motion

followed, the mobility remained restricted; elevation to a horizontal plane was possible. Two analogous cases were treated for rheumatism for a month. After this time following repeated attempts reduction by the abduction-elevation method was successful. The functional result in these 2 cases, which showed a fracture of the greater tubercle remained greatly impaired. A fourth uncomplicated case had the same course and result.

Five Weeks Old. Of 2 cases admitted five weeks after the injury, in 1, a woman, aged sixty-four years, reduction was possible after prolonged manipulations. The functional result was poor. In the other case, a farmer, aged seventy-four years, every attempt failed. He was discharged unimproved.

Six Weeks Old. The woman, aged sixty-two years, summoned the doctor after six weeks. By permanent extension (Hofmeister) an attempt was made to lengthen the contracted muscles around the dislocated head. This proved unsuccessful. The patient was discharged.

Two to Five Months Old. In a woman, aged sixty years, reduction was impossible after two months. Operation was contraindicated at this age. The patient complained for years of severe pains in her stiff shoulder when the weather was changing.

A woman, aged seventy-two years, and a man of the same age came three months after the injury. They were discharged unimproved, an operation being inadvisable at this age. A shoemaker, aged seventy-four years, had the same history and course.

A workman, aged forty-nine years, was operated *five* months after the accident. The wound healed *per primam*; but the motion remained greatly restricted.

In another, a laborer, aged fifty-eight years, seven months after the accident the head of the humerus was extirpated. Also in this instance the result was very unsatisfactory. Sometimes on younger individuals this operative procedure gives very good functional results.

These neglected cases illustrate very well the importance of an early accurate diagnosis controlled by roentgen-rays and subsequent rational treatment.

5. Conclusions. Our study shows that reduction by gentle manipulations by the Kocher method after a preliminary hypodermic injection of morphia will usually prove satisfactory. Proper reduction will be attained in the majority of cases without general anesthesia. Active and passive motion must be started immediately after reduction. No bandage is indicated. The patient should use his arm in his daily work. In a large series (157) of cases treated in this way (de Marbaix) no dislocation recurred. The time for complete cure with normal function therapy is greatly shortened (fourteen to eighteen days).

In neglected cases reduction is possible even after weeks. Finckh's

experience was that a dislocation of more than nine weeks' duration could only be treated by open reduction in the absence of any other contraindication (age). In our cases, delay in reduction always resulted in a permanent impairment of function.*

BIBLIOGRAPHY.

- Baumann, E.: Drei seltene Fälle von Schulterluxationen, *Beitr. z. klin. Chir.*, 1917, 110, 211.
- Finckh, J.: Ueber die Reponibilität der veralteten Schultergelenkluxationen, *Beitr. z. klin. Chir.*, 1897, 17, 751.
- Gubler, H.: Zur Prognose der Schultergelenkluxationen, *Schweiz. med. Wchnschr.*, Basel, 1922, 52, 960.
- Imbert and Dugas: Du pronostic éloigné des luxations de l'épaule, *Bull. Acad. de méd. de Paris*, 1910, 64, 84; *Rev. de chir.*, 1911, 43, 187.
- Iselin: Die Röntgenuntersuchung der Schulter in zwei zueinander senkrechten Richtungen, *Beitr. z. klin. Chir.*, 1915, 97, 473.
- Kaufmann, C.: *Handbuch d. Unfallmedizin*, 1919, 4th ed., 483.
- Körteweg: De gevolgen der schouderluxatie en haar nabehandeling, *Abstract, Zentralbl. f. Chir.*, 1916, 43, 926.
- Küttner: Zur Prognose der traumatischen Luxationen, *Verhandl. d. deutsch. Gesellsch. f. Chir.*, 1908, 1, 282.
- Lenormant: Les résultats fonctionnels éloignés dans les luxations de l'épaule, *Presse méd.*, Paris, 1911, 19, 192.
- Lexer, K.: Nachuntersuchungen von traumatischen Schultergelenksluxationen, *Beitr. z. klin. Chir.*, 1910, 70, 221.
- Marbaix, de F.: Funktionelle Behandlung der Schulterverrenkung, *Monatsschr. f. Unfallheilk. und Invaliden-wesen.*, Leipzig, 1913, 20, 241.
- Marbaix, de F.: Traitement de fracture du radius par la mobilisation immédiate sans réduction; application de la mobilisation imméd. au traitement de la luxation de l'épaule, *Jour. de méd. et de chir.*, Paris, 1910, 81, 882.
- Möltgen, M. H.: Zur Nachbehandlung der Humerusluxation, *München. med. Wchnschr.*, 1919, 13, 357.
- Schmidt, H.: Ueber die Prognose der Luxation Humeri, *Deutsch. Ztschr. f. Chir.*, 1911, 109, 20.
- Schulz: Zur Prognose der traumatischen und unkomplizierten Schulterluxation, *Beitr. z. klin. Chir.*, 1908, 60, 333.

REPORT OF SIX CASES OF CUTANEOUS ANTHRAX TREATED BY THE LOCAL AND GENERAL ADMINISTRATION OF ANTI-ANTHRAX SERUM.

BY JOSEPH C. REGAN, M.D.,

AND

CATHERINE REGAN, M.D.,

NEW YORK.

(From the Kingston Avenue Hospital, Department of Health, City of New York,
Frank J. Monaghan, M.D., Commissioner of Health.)

THE therapy of cutaneous anthrax has been for many years a much disputed question. The disadvantages and even dangers

* I wish to express my sincere thanks to Prof. Paul Clairmont, head of the surgical clinic at the University of Zürich for his courtesy in permitting the use of the histories of the cases.

of the measures of local treatment of malignant pustule in general use have been spoken of by one of us at length in previous articles. Suffice it to say here that these disadvantages include scarring, disfigurement, pain, the danger of secondary infection being introduced, liability of spreading the disease locally or into the circulation, prolongation of convalescence, lack of specific action and high mortality rates. The pustule is best left to its own evolution rather than to employ the more radical measures, owing to their tendency to disseminate and generalize the local disease, while the more palliative measures exert their action entirely too superficially for any direct curative effect.

The curative value of anti-anthrax serum should be regarded as established by the statistics now available. In the past the serum has in a great many cases been used in conjunction with some other measure of local treatment, which from our viewpoint was unnecessary and in many instances no doubt offset the efficacy of serum therapy. It must be remembered that anthrax in man is primarily a local infection with a decided tendency to remain as such in a high proportion of cases, and no method of treatment is warranted which tends to break down the barrier zone of the inflammatory process which Nature has so carefully and characteristically constructed in this disease. It is our belief that the local injection of serum provides a desirable means of therapy to replace the various methods that have been previously in common use, such as thermo-cautery, chemical cautery, incision, excision etc.

For the local injection, a Luer or Record syringe, 2 to 5 cc capacity, with a fine needle is used. The needle is inserted into the indurated border of the pustule just outside the eschar, and is directed fairly deeply (from 2.5 to 3.5 cm.) into the subcutaneous tissues at the base of the lesion. A total of from 6 to 12 cc of serum is injected, the needle being inserted at two or three points, and the serum given so as to circumscribe the pustule.

The injections are made once, twice and occasionally in very severe cases three times in twenty-four hours. Commonly in the usual case 4 to 6 injections suffice.

There is a slight increase in the inflammation following the first one or two local treatments, but within two or three days the lesion has usually decidedly improved, the induration and soft edema subsided, and after one week the eschar alone remains at the site of the pustule. Cultures taken after the first few injections of serum are given are almost always negative. The eschar itself spontaneously separates from the underlying tissue during the second or third week and the wound that remains quickly heals with only a minute scar, which is commonly invisible on superficial examination. The theoretical basis for the local use of serum has been discussed in the previous papers.^{2, 3}

The local injection is a supplementary measure to the general (intravenous, intramuscular, and subcutaneous) administration of serum. The essential aims in giving serum being (1) to bring about a subsidence of the local lesion; (2) to counteract whatever toxemia may exist; (3) to anticipate and prevent the development of an anthrax septicemia, or to control the same if it exists when treatment is begun.

The frequency of injection, the amount of serum given and the route of administration should, we believe, be graded according to the severity of the case. Thus the serum administered varies in amount from 40 cc in mild cases every twelve to twenty-four hours to 80 to 130 cc every six to eight hours in the more severe cases with voluminous lesions. In septicemic cases the dosage is still larger, 200 to 300 cc every three to six hours intravenously. During the first twenty-four hours of treatment, while awaiting the result of blood culture, if there is any question as to the severity of the case, and if there is the least possibility of septicemia, it is best to use large doses, 100 to 150 cc, given intravenously every six to eight hours. It is now a well-recognized fact that some of the most grave types of cutaneous anthrax may have little constitutional disturbance. Probably the one factor which should guide us most in the first day's treatment is the size of the lesion and extent of the soft edema, but even this is not an invariable index of the severity of the case. Symmers,¹ in reporting the successful treatment with recovery in a septicemic case, has recently emphasized the advisability of massive dosage until the result of the blood culture is known. The writers wish most emphatically to agree with Dr. Symmers' contention in the matter. After this initial twenty-four hours of treatment and with the blood culture findings at hand, one can then follow the plan of dosage outlined in previous papers by Dr. Eichhorn and one of the writers.

The anthrax serum used in this country is that prepared by immunization along the lines suggested by Dr. Eichhorn, formerly of the Bureau of Animal Industry, Washington, D. C. Immune serum thus prepared has been shown to be more potent than the European preparations.

Anthrax serum affords the most desirable method of therapy for anthrax for several reasons. It offers the least pain; a minimum of scarring and deformity; it is applicable to all forms and locations of the malady; it is a specific measure and a safeguard against generalization of the local disease if used in time. It has on an average the lowest mortality rate and necessitates a relatively short absence from employment. Recovery occurs without any serious complications or sequels.

Two cases of cutaneous anthrax which were successfully treated by the local and general administration of anti-anthrax serum have been previously reported.³ Subsequently in two later papers⁴

the advantages of the serum treatment of the disease as compared to the various commonly employed methods of therapy have been emphasized. The present paper includes the case reports of 6 additional patients who have recovered under local and general serum therapy; 6 other patients have also been cured, but the case histories are not included. In addition to this series of 14 successfully treated patients, we have 2, both of whom presented a septicemia on admission, and who died, 1 within twenty-four hours, the other within thirty-six hours of entrance to the hospital.

Case Reports. CASE I.—No. 3125. A young man, aged twenty-nine years, was admitted to the Kingston Avenue Hospital on December 23, 1919.

Present Illness. The first symptom observed by the patient was on December 21, when he noticed a small "pimple" on the right side of his neck. This was accompanied by slight local discomfort, weakness, malaise and later diarrhea. The lesion continued to grow larger until the time of admission to the hospital. The patient's occupation was that of a truckman and on December 17 and 18 he had been handling hides imported from China.

Physical Examination. The pustule is located on the right side of the neck in the submaxillary region, and measures 3 cm. in diameter. It consists of three zones: A central depressed cherry-black eschar, very tenacious, attached intimately to the underlying tissue, a white elevated border containing here and there a few vesicles oozing an occasional drop of serum and a red areola. Around the pustule is a hard indurated swelling measuring 6 cm. in diameter, and this in turn is surrounded by a soft edema, extending to the left side of the neck downward to the region of the trachea and upward to the lower portion of the face. The constitutional symptoms are not marked, the temperature, pulse and respiration being 100° F., 120 and 30. The heart, lungs and abdomen reveal no abnormality on examination. A blood count showed 17,000 white cells, with a differential count of 75 per cent polymorphonuclears, 23 lymphocytes and 2 large mononuclears.

Clinical Course and Treatment. December 23. On admission 38 cc of Eichhorn's anti-anthrax serum was given intramuscularly and subcutaneously in the left buttock, and 6 cc was introduced by local infiltration around the lesion, the needle being inserted at three points. December 24: The lesion is less active in appearance. There is no longer any oozing of serum from the vesicles, the induration is a little more pronounced but this is probably the result of the injection of the previous day. The general condition is improved; the temperature at 8 A.M. was 101° F., pulse 106 and respiration 28. At 10 A.M., 45 cc of anthrax serum was injected intramuscular and 8 cc of serum was given around the lesion. December 26: Pustule much improved, the inflammatory reaction surrounding

the lesion has practically disappeared as has also the blanched zone, leaving a flat black central eschar which is still intimately attached, and located in a small area of induration and edema. In the morning 32 cc of anthrax serum was given by intramuscular and subcutaneous injection and 7 cc of serum was infiltrated around the lesion. December 27: The lesion presents all the characteristics of one which is rapidly drying up, the tissues around the black central eschar having assumed a shrivelled appearance. The edema and induration are less. December 29: The lesion continues to dry up, the edema has practically entirely disappeared. The patient is able to be up out of bed. January 3: A multiform erythematous rash with slight arthritic pains, and some swelling of feet and hands has appeared and due to the serum. January 10: Eschar has spontaneously separated from the underlying tissue and with a forceps without any traction was removed. The base of the wound shows clean granulations. The edges were drawn together by adhesive plaster.

The patient was discharged on this day, and when seen two weeks later the wound had entirely healed, leaving a minute scar visible only on close inspection. The patient's general health was excellent.

Bacteriological Report. Cultures taken on admission from the serum oozing from the vesicles and by lifting up the margins of the eschar revealed a large Gram-positive bacillus, with square cut ends, occurring singly and in chains. The bacillus was non-motile. The colonies on agar plates were large dry, white, opaque with fringing projections. A few staphylococcus colonies were also present. Transplants from the large colonies gave a pure growth of anthrax bacilli showing spore formation. Inoculation of a culture into a white mouse produced death in twenty-four hours, and the same bacillus was recovered from the internal organs of the animal. In direct smears, it showed a capsule. All cultures from the lesion after the initial treatment were negative for anthrax.

CASE II.—No. 1927. A man, aged forty-six years, was admitted to the Hospital on September 15, 1920. Occupation was that of longshoreman.

History. On September 11, while working, the patient began to feel tired. He returned home, and shaved, in doing which he cut off the "head of a pimple" which he noticed on the right side of his face. During the following two days his face became swollen and inflamed around the site of the "lesion." He felt rather weak, but little pain was experienced at any time. On September 13 a crust formed on the lesion. On September 14 he called a physician who gave him a solution to apply. The swelling became worse and on the following day the doctor advised him to go to the hospital.

Physical Examination. The pustule is located on the right side of the face. It consists of three zones: A cherry-red, depressed, central eschar, firm and tenacious, measuring 3 cm. x 2.5 cm., a small narrow blanched zone measuring about 3 mm. and indefinite in places, and a red areola measuring about 5 mm. Around the pustule is a zone of induration, 6 cm. in diameter in most places. This in turn merges into a soft edematous swelling extending 9 cm. on the inner side reaching to and almost entirely closing the left eye, and on the outer side extending 6 cm. involving the left auricle and mastoid process. The lesion is not especially painful and is not sensitive to touch. The examination of the chest and abdomen are negative with the exception of an impairment of the muscular quality of the first sound at the apex. The general condition is fair. The temperature is 100° F., pulse 70 and respiration 24.

Clinical Course and Treatment. On September 15, at 8 P.M., 40 cc of Eichhorn's anti-anthrax serum was injected intravenously and 8 cc subcutaneously around the pustule, the needle being inserted at three points, 1 cm. outside the eschar, in the indurated zone. At 11.25 A.M. the patient had a fairly marked chill lasting fifteen minutes, following which he perspired profusely. In the afternoon the patient was feeling so much better that he wanted to sit up in bed and read the newspaper. There was considerably less soft edema present than on the previous day. September 17, 10 A.M.: 45 cc anthrax serum given by intramuscular and subcutaneous injection also 42 cc by the intravenous route and 8 cc around the lesion. Very marked improvement in the pustule is already evident, and the edematous and indurated zones are reduced in size. The patient's general condition is excellent and temperature has reached normal. September 18: 45 cc of anthrax serum given subcutaneously and 8 cc around the lesion. The pustule is improving rapidly, the blanched zone and red areola having disappeared, the soft edema has almost entirely subsided, the indurated border is shrivelled up and is much reduced in size. September 19: 35 cc of anthrax serum injected subcutaneously. September 22: The patient is now sitting up and the lesion has an entirely different appearance, in fact all that remains is the central eschar elevated above the surrounding tissue like a button. September 30: Eschar detached from the underlying tissue by lifting it up with a forceps. The base of the wound below looks fairly clean and has almost filled up to the level of the skin with healthy granulations. October 3: Wound clean; no discharge; margins drawn together by adhesive plaster. October 6: Patient discharged, the lesion being almost healed. The wound healed within a week afterward and a minute scar visible only on careful inspection remained.

Bacteriological Report. All blood cultures were sterile. The culture of the wound taken a few hours after admission showed a

large Gram-positive bacillus corresponding in its morphological and cultural respects and its pathogenicity to the organism isolated in Case I, and therefore anthrax. All subsequent cultures taken after treatment was started were negative.

CASE III.—No. 1015. A man, aged forty-eight years, was admitted to the hospital on April 17, 1920. His occupation was that of a scaleman in warehouse for hides.

History. On April 9, while sitting beside a fire, a spark was blown onto the skin of his neck producing a small blister. The same night he shaved and in doing so cut the blister. He continued to go to work until April 16, during which time the pimple which had appeared gradually became larger and a serous fluid continually oozed from it. On April 16 he began to experience some difficulty in swallowing and felt for the first time very sick. At this time he was seen by a physician who said he had a boil. The following day he was much worse with headache, chills and perspiration, and was transferred to the Wyckoff Heights Hospital where a diagnosis of anthrax was made and 40 cc of Eichhorn's serum was administered by the intramuscular route. He was then transferred to Kingston Avenue where he was seen by Dr. Eicher and the writers.

Physical Examination. Patient is rational, but complains of pain in his neck, and states he has difficulty in swallowing and that his voice is hoarse.

On the right side of the neck about 2 inches below the angle of the jaw and on a line with the sternocleidomastoid muscle there is a large angry looking lesion, elevated above the surrounding tissue and measuring about 4.5 cm. x 3 cm., rather elongated and comprised of a central cherry-black eschar, grayish-white vesicular rim, and red areola. Puncture of the vesicular border causes a serous exudate to pour out. Around the pustule is a hard brawny swelling measuring 1 cm. at the upper and inner margins of the lesion and 3 to 5 cm. at lower and outer borders, and of an erysipelatoid appearance. Beyond this there is a soft edema extending below to the fourth rib on the right side, and posteriorly to the median line of the neck.

The chest and abdomen were negative with the exception of a faint systolic murmur at the apex. A blood count taken on admission showed a total leukocyte count of 13,300, differential: polymorphonuclears, 86 per cent; lymphocytes, 13 per cent; eosinophiles, 1 per cent. The temperature was 103° F.; pulse, 90 and respiration, 26.

Subsequent Clinical Course and Treatment. April 17: At 10.30 P.M., 26 cc of anthrax serum was injected intravenously and 6 cc of serum was given around the lesion. At 11.20 P.M., the patient had a rather severe chill with some cyanosis and lasting about

fifteen minutes. This was followed by profuse perspiration. April 18: The patient's general condition is very much improved, and the temperature is normal. He has no complaints and states that he feels much better in every way. Forty cc of serum was given subcutaneously and by intramuscular injection and 8 cc was infiltrated subcutaneously around the lesion. April 19: At 12.50 P.M., 17 cc of serum was injected intravenously and 7 cc was given around the lesion. The total leukocyte count just before the administration of serum was 13,600, while at 1.45 P.M. it was 9000, and the white cells were clumped despite thorough shaking. At 3.15 P.M. it was 16,000 and at 6.30 P.M., 12,800. April 20: 40 cc of serum was administered by the intramuscular and subcutaneous routes, and 8.5 cc by local injection. The lesion is rapidly drying up and the indurated zone and the edema are rapidly diminishing in size. April 21: The pustule is now on a level with the surrounding skin, the vesicular zone and the red inflammatory areola have disappeared leaving the dry, central reddish-black eschar with an indurated zone which has shrunk greatly, measuring now only 1.5 cm. at its widest point. The induration is of softer consistency, and has lost its red color. The soft edema is almost gone. The tumor no longer stands out on the neck as a bulging mass as it did four days ago. April 23: 20 cc of anthrax serum given by intramuscular injection. April 26: 3 cc of serum injected locally. April 28: Continued improvement. The patient has been sitting up out of bed for the last few days. Some induration has reappeared at the upper part of the lesion and a small amount of creamy pus can be pressed out of this area. A small incision was made into this superficial abscess, the pus evacuated, and packing inserted, a wet dressing of 1 per cent chlorazene being applied. April 28 to May 11: The patient is in excellent general condition, and is up and around. The wound is clearing up. May 18: The wound is entirely healed. The skin over it is of a good healthy color and there is just a slight thickening, but no scarring. May 19: The patient was discharged in excellent physical condition. He was seen subsequently at long intervals and there was no sequels from his attack and the scar left was almost invisible.

Bacteriological Report. The smears taken at the Wyckoff Heights Hospital and at Kingston Avenue Hospital on admission showed a small number of bacilli which were very large, Gram-positive, and with square cut ends, morphologically identical with anthrax. Cultures were negative after admission, but clinically the case was beyond all question one of malignant pustule and the history of exposure was clear. This was further proven by the results of treatment with anti-anthrax serum.

CASE IV.—No. 739. A man, aged twenty-seven years, was admitted to the hospital March 12, 1920.

History. The patient is employed in a brush factory in which shaving brushes are manufactured, his duties being to clean out the loose hair after the brushes are made. On March 7 he noticed a "boil" on the right side of his neck. On the following morning he consulted a physician, who advised operative interference. The boil was incised, a dressing applied and he went home. The pustule became rapidly worse and an extensive edema appeared involving the neck and lower portion of the face.

Physical Examination on Admission. The patient does not appear to be severely ill. The pustule is located on the right side of the neck just below the inferior maxilla and presents a lesion of a peculiar appearance, consisting of a central black eschar measuring about 1.5 cm. perforated in its central portion by several sieve-like openings. The eschar crust appears to cover a hollow dry cavity. Around the eschar is an indurated zone measuring about 3.5 cm. in diameter which is in turn surrounded by an area of soft edema extending upward to the right cheek and downward almost to the clavicle. The margins of the eschar are deeply adherent to the neighboring tissue and can be detached only with the greatest difficulty. A blood count taken on admission showed 11,400 leukocytes, with a differential count of 87 per cent polymorphonuclears; 12 per cent lymphocytes, and 1 per cent large mononuclears. March 12: At 9 P.M., 30 cc of anthrax serum was injected by the subcutaneous and intramuscular route. March 13: At 4 P.M., 35 cc of anthrax serum given by the same route, also 8 cc injected locally into the indurated tissues around the eschar. March 14: There is more inflammatory reaction in the pustule. The indurated area is slightly more extensive and more deeply red in color. At 5 P.M., 8 cc of serum injected locally and 30 cc intramuscular and subcutaneous. March 16: The edema around the lesion is almost entirely gone, but the induration is still present; 10 cc of serum administered by local injection. March 18: Induration still present around the lesion but the skin is becoming wrinkled. General condition of the patient is good. March 20: 8 cc of anthrax serum injected locally into the indurated margin of the eschar. March 21: Eschar crust can be loosened up at its margins, and beneath there is a profuse purulent secretion, evidently due to a secondary infection as cultures show a staphylococcus, which may have been introduced with the initial surgical incision. March 26: Lesion improving rapidly, induration and inflammation have disappeared with the exception of the right side of the wound. The eschar has spontaneously separated. March 28: The wound continues to improve the discharge becoming progressively less and the healthy granulations covering the ulcer. March 29: The margins of the wound were drawn together by adhesive and the patient was allowed to go home. The wound healed entirely within about one week after discharge, leaving a minute almost invisible scar.

Bacteriological Report. Cultures from the wound taken on admission were negative for anthrax. Yet clinically there could be no question of the diagnosis, and the inability to find the organism in the superficial portions of the pustule was no doubt due to the early surgical treatment before the case came under observation.

CASE V.—No. 2414. A man, aged thirty-three years, was admitted to the hospital on December 8, 1920, with a diagnosis of anthrax. Occupation is that of a truckman, in which work he often handles imported hides.

History. Patient noticed a small pustule on his right arm eight days before admission. He paid no attention to it until December 3, when he began to feel very ill, had chills of a severe type, one after another with high fever and delirium at intervals. These symptoms continued on the following four days the lesion meanwhile growing larger and becoming a very blue color.

Physical Examination on Entrance. The pustule is located on the palmar aspect of the forearm just below the bend of the elbow; it consists of two zones: A cherry-red-black central eschar measuring 2.5 cm. in diameter with a surrounding red elevated border. The lesion is situated in the center of a marked edematous swelling which extends on either side for almost 9 cm. General examination otherwise was negative, with the exception of a slight impairment of the myocardial element of the first sound at the apex.

Subsequent Clinical Course and Treatment. On admission the patient was seen by Dr. Charles Sherry of the resident staff and 40 cc of Eichhorn's anti-anthrax serum was given intravenously, 30 cc intramuscular and 13 cc around the lesion, cultures having been taken previously from the pustule and from the blood. December 9, at 3.30 P.M., an intravenous injection of 40 cc of the serum diluted with 60 cc of sterile physiological saline was administered. At 5 P.M. 18 cc of serum was given around the lesion. December 10: At 12.30 P.M., an intravenous injection of 25 cc of the serum in 25 cc of sterile normal saline was given, also 40 cc of serum was injected intramuscularly and subcutaneously. December 11: The lesion is little changed, the edema persists also quite some induration and a fairly marked inflammatory reaction with redness and slight pain is present for several inches around the lesion, evidently due to the serum. Wet chlorazene dressing (1 per cent) applied. Patient's general condition excellent, fever has entirely subsided and he feels fine. At 4 P.M., 50 cc of serum in 50 cc normal saline given intravenously, and 10 cc injected locally. December 13: Lesion very much improved; the inflammatory reaction due to local injections of serum has disappeared. The redness, edema and swelling have all subsided. At 11 A.M. 55 cc of serum given subcutaneously, and at 5 P.M., 75 cc in 30 cc sterile physiological saline intravenously. December 14: At 3 P.M., 50 cc of serum in

50 cc of sterile physiological saline injected by the intravenous route. December 15: 40 cc of serum by subcutaneous injection. December 16: Lesion is rapidly drying up, and very little induration remains; the tissues about the eschar have assumed a shrivelled appearance. December 21: Patient able to be up and around. December 29: Eschar has in the last few days spontaneously separated and come out; base of the wound presents healthy granulations. January 3, 1921: Edges of ulcer strapped together and patient discharged. January 17: Patient seen, wound has been healed for almost a week. There will be, if any, only a minute scar. General health excellent.

Bacteriological Report. The blood culture of December 8, while negative for growth by transplants presented on direct smears of the glucose broth a few bacilli morphologically like anthrax. The culture of the lesion taken on admission gave a pure growth of bacilli, typical in all respects of anthrax and having the same cultural characteristics and pathogenicity as that isolated in Case I. All subsequent cultures from the pustule were negative.

CASE VI.—This patient was treated by Dr. Claude Almond, formerly of the resident staff of the hospital and he has kindly consented to the inclusion of a brief reference to it in the present report.

CASE No. 2241. A young man, aged eighteen years, was admitted to the Kingston Avenue Hospital August 2, 1919, with a diagnosis of anthrax.

History. On July 26, the patient noticed a small papule just at the margin of the hair above the left eye. The swelling around the papule gradually enlarged, and by July 31 the entire left side of the face was involved. Just before the papule appeared he had used a new shaving brush which had been recently purchased.

Physical Examination. The pustule is located above the left eye, and measures 4 cm. in diameter. It has a well defined areola and two distinct vesicles at the margin of the lesion. These latter are oozing a serous fluid at intervals. There is a thick dark eschar covering the lesion and it is somewhat depressed in its center. The tissues around the pustule show some induration. There is a soft edema of the left side of the face and neck with moderate enlargement of the cervical lymph nodes.

Treatment. August 2: 20 cc of anthrax serum by intramuscular injection, 8 cc around the lesion. August 3: 20 cc anthrax serum intramuscularly, and 7 cc around the lesion. August 4: 30 cc of anthrax serum intramuscularly, and 7 cc locally injected at the base of the eschar. August 6: 20 cc of anthrax serum intramuscularly. August 6: 12 cc of anthrax serum injected locally. August 10: 28 cc of serum by the intramuscular route, and 8 cc locally.

Clinical Course. By August 4 the pustule was beginning to diminish in size and to dry up. On August 6 the induration

around the lesion had disappeared, as also had most of the soft edema. The lesion continued to improve and the eschar spontaneously separated on August 15. On August 22 the lesion had practically healed over. The patient was discharged on August 27, with no sequels, practically no scarring, and in very good condition.

Bacteriological Report. Blood cultures were negative. Cultures from the wound on admission gave a growth of large Gram-positive bacilli corresponding in all respects to those described in Case I, and evidently anthrax.

Conclusions. The local and general administration of anti-anthrax serum is the most logical, effective and specific method of treatment for cutaneous anthrax that can be employed. It possesses less objectionable features, and none of the dangers of the methods previously in common use. It may be relied on to cure every case of malignant pustule if the patient is not suffering from some chronic debilitating disease and comes under observation before septicemia has already developed. Even in the latter instance, it is the one method that offers the slightest chance of a success and therefore should always be tried.

Two cases treated by this method have been previously reported; in the present paper 6 other cases are included, all of whom recovered. We have, in addition, records of 6 more patients who were treated in a similar manner and in whom recovery ensued. This makes a total of 14 recoveries with serum therapy. We have had 2 failures in our experience, both patients coming under observation within less than forty-eight hours of death and with an anthrax septicemia already well developed on their admission to the hospital.

BIBLIOGRAPHY.

1. Symmers, D.: *Ann. Surg.*, 1922, 75, 663.
2. Eichhorn, A., Berg, W., and Kelser, R.: *Jour. Agricul. Res.*, 1917, 8, 37.
- Eichhorn, A.: *Jour. Am. Vet. Med. Assn.*, 1916, 48, 669.
3. Regan, J. C., and Regan, C.: *AM. JOUR. MED. SCI.*, 1919, 157, 782. Regan, J. C.: *Jour. Am. Med. Assn.*, 1919, 72, 1724.
4. Regan, J. C.: *AM. JOUR. MED. SCI.*, 1921, 162, 406; *Jour. Am. Med. Assn.*, 1921, 77, 1944.

SYPHILIS OF THE HEART AND BLOODVESSELS.

By TASKER HOWARD, M.D.

BROOKLYN, N. Y.

THE importance of the subject of syphilis of the heart and blood-vessels depends upon several factors: Its frequency, its high mor-

talities and the fact that, untreated, it is usually progressive, while if properly treated it may often be controlled. Its frequency is attested both at the autopsy table and in the clinic. Brooks¹ found fatal circulatory failure directly attributable to syphilis in two-thirds of 50 consecutive autopsies on syphilitic subjects. Clinically we find from 30 to 60 per cent of all cases of aortic regurgitation and practically all cases of aortic aneurysm are due to syphilis, while many cases of angina pectoris fall in the same category. The mortality of these conditions is too well known to require comment. In the study of 100 syphilitic patients from a syphilis clinic, I have found 40 per cent showing cardiac abnormalities.² Many of these abnormalities disappeared under treatment, particularly in the early cases. Even the more serious later involvements frequently respond very satisfactorily to specific treatment. This is not without its dangers. Routine "anti-syphilitic treatment" of these patients often ends in disaster. Wile³ believes that the arsenical preparations are too dangerous to use at all, and advises urologists not to undertake the treatment of such patients without the coöperation of an internist. It seems to me that much of value would be lost if we discarded the use of the arsphenamine preparations entirely; but they should be used very cautiously, the dose being minimal, and the patient kept in bed and watched very carefully.

Before taking up the clinical side of the subject may I present briefly what happens to the tissues of the circulatory system in the course of a syphilitic infection? Early in the disease, there is a widespread distribution of the invading organism. At this time there is apt to be a little fever, and visible lesions due to the presence of the treponema appear on the skin and mucous membrane. But few autopsies have been performed at this stage of the disease, but it has been conclusively shown that even thus early, the offending organisms are found in the heart and aorta. Parenchymatous degeneration is seen in the muscle, and about small branches of the coronaries and vasa vasorum of the aorta there have been found little collections of lymphoid and epitheloid cells. Brooks describes perforation of the aorta through a luetic lesion at this stage (*loc. cit.*). There follows fragmentation of the muscle fibers and proliferation of the fixed connective-tissue cells with ultimate scar formation. Within the aorta such processes are said to begin in the adventitia and outer layers of the media, working toward the intima, which ultimately becomes thickened and hyaline. It is such weakened areas that give way under the pressure within the vessel and bud out into aneurysms. Involvement near the root of the aorta usually involves the aortic valve, giving rise to aortic regurgitation. The

¹ AM. JOUR. MED. SCI., 1913, 146, 513.

² *IBID.*, 1922, 163, 64.

³ *IBID.*, 1922, 164, 415.

orifices of the coronaries are many times partially blocked with consequent myocardial degeneration of a secondary nature. The smaller vessels, as most typically seen in the brain, are the seat of perivascular infiltration, with involvement of the vessel wall, thickening, obstruction of the blood flow and formation of miliary aneurysms. These changes are usually late in their development. I have seen a tiny aneurysm of syphilitic origin in one of the retinal arteries.

Clinically, cardiac involvement may often be recognized early in the disease if it is looked for. Of 50 syphilitic patients, whom I examined during the secondary stage, 8 complained of palpitation of the heart, 5 of cardiac pain and 3 of dyspnea. One had edema. Cardiac dilatation may often be made out, and the heart is often found to be overacting, as in fever, with throbbing carotids, and possibly an occasional extrasystole. A common sign is reduplication of the second sound at the apex. Such signs mean syphilitic invasion of the myocardium and require some consideration in the treatment. It is obvious that the most important indication is the eradication of the infection, as promptly as possible, which means a vigorous course of arsphenamine and mercury. It should be remembered, however, that a full dose of arsphenamine may give a local cardiac reaction in the form of increased symptoms and it is wiser to begin with small doses, say, 0.3 gm. of the milder neoarsphenamine. Such a patient should then be decidedly limited in his activity and should be confined to bed for at least twenty-four hours after each arsphenamine injection until the cardiac symptoms have abated.

This type of case is perhaps, the most important of any, because at this stage there is every reason to believe that serious cardiac vascular syphilis may be prevented.

An example of early myocardial involvement is the case of E. M. He was a watchman, aged twenty years, who had no previous illness except mumps. Three months before admission he had developed a primary sore. About eight weeks after this he had noticed sore throat and cutaneous eruption. Shortly afterward he began to complain of precordial pain and palpitation on exertion or excitement. When I first saw him he had received five weekly injections of mercury salicylate. At this time he still showed a fading eruption on the arms and trunk and a general adenopathy. His heart extended 3 cm. to the right, 17 to the left, reaching the anterior axillary line. There was a systolic murmur at the apex, which was not transmitted until after exercise when it was louder and could be heard in the axilla. The second sound was reduplicated at the apex. There was a cardio-respiratory irregularity only, and the rate was not elevated. He showed no signs of venous stasis. With rest and continued mercurial treatment, his symptoms practically disappeared in the course of a month, and the transverse diameter decreased from 20 to 15 cm.

Perhaps the commonest and most typical cardiac lesion of syphilis is aortic regurgitation. The figures on the relative frequency with which this lesion is due to syphilitic and rheumatic infections differ considerably. In our series of 100 cases at Long Island, only 36 per cent were syphilitic. This is considerably lower than is usually given. At all events syphilitic régurgitation is a common disease. It usually is discovered years after the original infection. In fact many times the patient is quite unaware that he has syphilis. The disease may be roughly divided clinically into two stages, the first being without symptoms, or with such minor complaints as a little palpitation or throbbing in the neck and head on exertion, while the second stage is characterized by the development of dyspnea and edema. The distinction is really a very vital one, as the transition from the first to the second stage signifies, as a rule, that there has been sufficient specific involvement of the myocardium to interfere with its proper function. Specific treatment in either case may check the progressive syphilitic process, but in the case of patients in the first stage they are left with sufficient myocardial margin to meet even the increased demands of a leaky valve, while patients in the second stage have already lost their margin of safety and possibly more besides. The heart muscle does not regenerate and scar tissue is useless. The case is not altogether hopeless however, for patients who have developed symptoms. Proper rest and conservation of the muscle that they *have* left may reinstate them into the first stage, and specific treatment, by preventing further damage, offers some hope of keeping them there for a very considerable period.

To consider in some detail the treatment of these patients, let us first consider the case of a patient with a clean-cut diagnosis of syphilitic aortic insufficiency but without symptoms. His circulatory system will require no non-specific treatment; but it is of course advisable to caution him against putting undue strain upon his heart by violent exercise. The specific treatment should ultimately be as thorough as possible, but in the earlier stages it is well to remember the chances of a local reaction which may prove disastrous. I believe it is safer to begin with small doses of mercury, using from $\frac{1}{2}$ grain to $1\frac{1}{2}$ grains of one of the insoluble salts weekly by intramuscular injection. The patient should be seen two days after each injection and promptly put to bed with the first suspicion of myocardial failure. After six or eight weeks of mercury, one may turn to arsenic. Here again the danger of a reaction must be borne in mind—0.2 gm. of neoarsphenamine is quite large enough for the first dose. The patient should receive the injection in bed and stay there for twenty-four hours. If he shows no reaction the next day he may be allowed to get up. After a week the dose may be doubled. The third week a full dose may be given, if no reaction is observed, and thereafter arsphenamine

may be used as it is more potent than neoarsphenamine. No cardiac reaction is likely to be observed after this period. If a reaction is encountered while working up to the maximum dose, the patient should be kept in bed, and smaller doses used after it has passed off. When it is established that the patient tolerates specific treatment well, he should be treated like any other syphilitic with alternating courses of 6 or 8 arsphenamine injections and 8 to 12 mercury injections, or inunctions if you prefer, with periods of rest from all treatment, and attention to his general condition like any other patient. Periods of potassium iodide or mixed treatment may prove helpful. A negative Wassermann should be the goal, but of course, if it is not reached, one cannot keep up the treatment indefinitely and it is not necessary.

In fact, it is well to caution the patient at the start that the Wassermann may prove refractory, but that if he takes sufficient treatment, the Wassermann may ultimately be disregarded. If I were such a patient, I should prefer to have 5 or 6 courses of arsphenamine, with mercury in between, stretched over about three years, and would be content thereafter with an occasional course of mixed treatment.

I am afraid I can offer no illustrations of the first type that would be worth recording. Such patients are usually lost track of. The prognosis is, of course, doubtful, but it is certainly better than before we learned of the syphilitic nature of the disease. The patient is left with an aortic leak but its progressive character is at least considerably checked.

A much more difficult problem is presented in the case of a patient with syphilitic aortic regurgitation who has developed symptoms of broken compensation. The outlook is notoriously unfavorable and yet sometimes a good deal can be accomplished. Under such circumstances the specific treatment has to be postponed until the heart is doing reasonably well and even then it must be administered with the greatest caution. In the presence of dyspnea and edema, absolute rest in bed is, of course, indicated. Some form of opium is usually indispensable. Strict limitation of fluid intake will help to get rid of the edema and digitalis is of great help in slowing down and strengthening the cardiac action. If the patient can be made reasonably comfortable it is time to consider the utilization of specific medication. Under such circumstances, must we ever say, "This heart is too bad to attempt any specific treatment?" Personally, I think it is always worth the attempt, if carried out judiciously. In such cases I begin with small doses of mercury and iodide by mouth, keeping the patient in bed. The dose of the mercury can be gradually increased if well tolerated. After a month or so of this treatment, 0.1 gm. of neoarsphenamine may be given intravenously and this may be gradually increased at intervals of four days, up to 0.3 to 0.4 gm. I should hesitate to give larger

doses to a patient who had recently shown a break in compensation. The medication should be given in bed and the patient should stay there for at least twenty-four hours, being seen the next day. Throughout this period, tonic doses of digitalis should be administered and the patient should be under very strict observation. After 6 or 8 doses of neoarsphenamine, the mercury should be resumed, and may be given by inunction or the needle, but the dose should be moderate and the effect carefully watched. Such a patient requires much more restriction of activity and smaller doses throughout the course of treatment.

The outcome is certain from the start, but I believe carefully treated cases live longer than those who receive no specific medication.

May I quote the case of Mrs. A., seen first two years ago. She was thirty years old, the mother of one healthy child and did not remember ever having been sick in her life. Six months before she had had a period of pain in her left arm, attributed to neuritis. She had gradually been getting short of breath and six weeks before began to be troubled with a hard dry cough. She had recently got but little sleep because of cough and dyspnea, and for three days her legs had been swelling. She had lost 17 pounds in weight. She presented the typical signs of aortic regurgitation, with a weak, rapid heart action, the rate being 118. The lungs showed rales at the bases and her respirations were 36 to the minute. The liver was three fingers breadths below the costal margin. Her Wassermann was 4+. After four days of digitalis and codeine she was sleeping well and breathing easily, and the signs of passive congestion had largely cleared up. The codeine was needed only a few nights more, but she continued to take small doses of digitalis for months. The fourth day she was put on mixed treatment (bichloride of mercury, gr. $\frac{1}{12}$; potassium iodid, gr. 10) and this was kept up for two months, six weeks of it being spent in bed. Her general condition improved very markedly but she occasionally complained of pain the left wrist and arm and left side of the neck. She was then given 8 weekly injections of neoarsphenamine (0.1 to 0.2 gm.). This was followed by a course of mercury intramuscularly, a month's rest from treatment and three repetitions of the whole course, using gradually larger doses. She now leads a practically normal life, simply avoiding overfatigue and lying down an hour or so each day. Had she indulged in the amount of exertion which most of our hospital patients do, when they are sent home, no doubt she would have broken down long ago. The question may be raised as to what was accomplished by the specific treatment after all. It certainly has not given her any new heart muscle or restored the damaged valve, but may we not believe that it has at least partially checked the inroad of the disease into hitherto undamaged muscle? The neoarsphenamine has certainly accomplished at least one thing

each time and that is elimination of the pain, which tended to recur for a long time. This is not an uncommon experience in such cases.

Pure syphilitic myocarditis late in the disease is not an uncommon occurrence. Its three common manifestations are myocardial insufficiency, angina pectoris and heart-block. Myocardial insufficiency with aortic regurgitation has just been described. All the signs of failing heart are sometimes seen as a result of uncomplicated syphilis of the heart muscle. This condition responds much more readily to treatment than is the case with associated valvular defect. The conditions may be identical so far as the muscle is concerned, but a heart with a leaky valve requires better than normal muscle to compensate for the leak, while the heart not so handicapped has some margin of safety. The treatment therefore, may be bolder and better results may be expected.

An example of this type is found in Mr. G., an active man, aged fifty-five years, whose previous history is unimportant, and who denied venereal disease. He had complained of headache and bloody discharge from the nose for six months. He had also suffered some indigestion. Six weeks before he had begun to get short of breath and his legs had swelled for a few days. Examination showed a man with a lump on his forehead, an obstructed nose with a bloody discharge, double pleural effusion, ascites, and edema of the legs. His heart was much dilated (2.5 x 15 cm.) but showed no evidence of valvular disease. His blood-pressure was 130/78 and his urine contained a trace of albumin, the specific gravity being 1026 (kidney of passive congestion). The Wassermann was 4+. He was put on a dry diet, digitalis and potassium iodid with appropriate local treatment for the nose, advised by a rhinologist. The pleural effusions and dependent edema cleared up promptly but the ascites tended to persist. After a week he was given 1 mercury injection and about a week later 0.3 gm. of arsphenamine. Thereafter he was given a full course of the latter, followed by mercury inunctions and large doses of potassium iodid. In six weeks he was back at work. That was six years ago and he is still actively at work.

Angina pectoris due to syphilitic involvement of the coronaries or aorta is said to be not uncommon. I do not happen to have seen the former but have encountered the latter a number of times. The pain, anginoid or simple substernal distress, that so often accompanies aortitis, responds very satisfactorily to arsphenamine treatment.

Heart-block has been described a number of times as the result of a gumma or syphilitic degeneration of the bundle of His. The pathologists rank it as a cause of block more often than the clinicians, because it is readily found at autopsy and strikingly enough to be reported. Clinically, syphilis is comparatively rare as a cause of block. When it is found the block is seldom broken by anti-syphilitic treatment; but the treatment should be given to

check further involvement if possible, even though the offending lesion proves intractable to treatment.

Turning to the aorta, it will be recalled that syphilis invades this vessel early and often. During the secondary stage the treponemata tend to localize in the lymph spaces about the vasa vasorum. Here they may start a process so acute as to give rise to symptoms immediately, or as is more commonly the case, the process is so insidious that months or years pass before it makes itself manifest. In fact, it may remain latent throughout life, and never give any symptoms. It is supposed that latent syphilitic aortitis may account for the persisting Wassermann reaction which so often outlasts all symptoms. This seems reasonable when it is recalled with what confidence one turns to the aorta at autopsy in the case of a known syphilitic for the characteristic specific changes.

The symptoms of aortitis vary somewhat with the acuteness of the process. The most characteristic is *pain*, felt usually beneath the sternum, aggravated by anything that tends to raise the blood-pressure. The pain sometimes assumes the characteristics of a true angina. In the acuter forms there may be a little fever and some loss of weight, the patient being evidently ill. In the more chronic forms this side of the picture is lacking. There may be dyspnea, both on exertion or paroxysmal in character, which has been shown by Longcope to be of the reflex origin, depending upon irritation of the intima of the aorta. With these symptoms one finds evidence of valvular disease lacking, but there is a peculiar ringing accentuation of the aortic second sound, with possibly a systolic murmur over the aortic cartilage, transmitted into the neck. The area of aortic dulness is usually demonstrably widened and roentgen-ray plate shows quite early some dilatation and possibly increased density in the aorta. In this type of case, brilliant results are obtained by specific treatment, and one may have the satisfaction of feeling that the development of aneurysm has been prevented. The treatment, as always in cardiac vascular syphilis, should be begun cautiously, but in the absence of untoward reactions, it may be increased soon to maximum doses, and should be continued with all the thoroughness that syphilis always demands.

Aortitis with aneurysm superadded is a much more serious situation. When a weakened spot in the main arterial trunk gives way and starts to bulge, something has started that leads to certain destruction unless it is somehow checked. The pathologist long since showed us how Nature sometimes succeeds in checking the development of an aneurysm through the deposition of layer after layer of clot within the sac, the clots becoming more or less organized and reinforcing the weakened aneurysmal wall. This is the process which must be borne in mind, whatever else is done about the situation—and much else may be done. And so, when you encounter the syphilitic patient with a brassy cough, the husky

voice, the substernal pain, with a pulsating mass in his chest and perhaps signs of pressure on this neighboring organ or that, two lines of treatment present themselves to you: one the endeavor to bring about clotting within the sac, and the other, direct attack upon the syphilitic process. The former is best accomplished by means of the old Tufnell treatment or some modification of it. This consists of strict rest in bed with limitation of both fluids and food. In large saccular aneurysms, perhaps wiring and electrolysis should be tried as advocated by Hare. I believe specific medication should always accompany this treatment, and should be carried out in about the same manner as that outlined in the case of aortic regurgitation with broken compensation.

Through the courtesy of Dr. D. W. Waugh, I should like to report the case of a man whom I first saw while associated with him thirteen years ago. Mr. B. was at that time forty-four years of age. He had had smallpox and yellow fever but denied venereal disease. For a year he had had substernal pain radiating down both arms, and made worse by exertion. It had been growing gradually worse and had become so severe that he got but little sleep at night. He could not lie on either side. He had a cough and was hoarse. Examination showed a slight pulsating fulness in the left interspace, over which could be felt a thrill, and a soft murmur was heard which was audible in the back as well. Dr. Arrowsmith reported paresis of the left vocal cord, and fluoroscopy revealed the presence of an expansile tumor in the mediastinum, corroborated later by a plate. His Wassermann reaction was positive. He was kept in bed on a limited diet for seven weeks, during which time mercury and iodide were given by mouth. The pain practically disappeared in about two weeks though he had periods of some return of the pain for several months. After three months he returned to work and got along very well for about five years. At this time he developed violent pain in the back, radiating around both sides of the chest. At this time his Wassermann reaction was 4+, his spinal fluid being negative. Another roentgen-ray showed practically no change in the condition. He was kept in bed for three weeks and was given one dose of arsphenamine, but he refused to take any more and was therefore again placed on mercury by mouth and large doses of iodide. The pain promptly cleared up, and in the seven years which have elapsed since that time, he has only had occasional periods of mild pain which are quickly controlled by mixed treatment.

Syphilitic disease of the cerebral vessels usually comes to our notice in the form of thrombosis, involving most commonly the middle cerebral artery or some of its branches. It results most typically in hemiplegia, with or without aphasia, coming on rather gradually. If there is complete occlusion, the hemiplegia will be permanent, but partial occlusion may result in more or less transient

or incomplete palsies. In any event treatment is most unsatisfactory.

Conclusion. The fact should be emphasized that a great gain has been made in the recognition of the syphilitic nature of many cases of aortic insufficiency, aneurysm and myocarditis, and that appropriate treatment of these cases from this point of view, offers them a far better chance of comfort and prolongation of life.

RHEUMATOID ARTHRITIS WITH REMARKS ON THE USE OF COLEY'S TOXIN IN THE TREATMENT OF THIS CONDITION.

BY ROBERT TORREY, M.D.,

AND

THOMAS KLEIN, M.D.,

PHILADELPHIA.

(From the Medical Department of the Philadelphia General Hospital.)

THERE are many classifications of the chronic diseases of the joints and much confusion exists in the nomenclature of these conditions. Reports of series of cases of arthritis, chronic rheumatism, rheumatic gout and allied conditions leave us in doubt as to what condition or disease has been under discussion. Particularly deplorable is the confusion which exists in the consideration of rheumatic fever as an acute arthritis which may go on to a chronic arthritis, eventually becoming arthritis deformans or chronic rheumatism. This view is a common one, much more common than most of us realize, and is unfortunate because through it the danger of rheumatic fever which is entirely a question of cardiac damage is overlooked, while attention is focussed on the joint. Also the serious aspect of an early rheumatoid arthritis may be ignored if the case is considered as one of mild acute rheumatism or rheumatic fever.

As McCrae¹ has stated, it is difficult to make an absolute separation of cases of chronic deforming arthritis into hypertrophic and atrophic forms, as there may be an overlapping of both these tendencies in a given case; but it will be found that most cases of generalized or multiple chronic arthritis show a definite tendency toward certain general characteristics which serve to place them in one or the other of these classes. No purpose can be served by an endeavor to augment the existing classifications which are already too numerous and too complicated, but a simple tabulation of the most frequent descriptive or classifying terminology may simplify the picture of these conditions.

Rheumatic Fever. This disease does not tend to become chronic; exceptionally where infection is persistent in the pericardium, fre-

quently repeated exacerbations recur with a simulation of chronic arthritis. Also where secondary streptococcic infection of the valves is present with bacteriemia, recurrent joint infection may take place. In either of these conditions the cardiac picture will properly place the disease. Otherwise rheumatic fever has nothing in common with chronic arthritis. The cardiac effects of rheumatic fever are of profound importance; the importance of the arthritis is negligible. When recovery takes place recovery is complete. There is little or no permanent atrophy and no bony change, contractures and fibrosis are not serious, and the joint is functionally as good as ever.

This condition must be sharply separated from chronic arthritis and is discussed in this connection, only for the purpose of emphasizing this distinction.

I. Chronic Arthritis. Arthritis Deformans.

Chronic Arthritis	} Arthritis Deformans	Atrophic
Primary Progressive Polyarthritis		(Rheumatoid Arthritis)
Chronic Non-suppurative Arthritis		
Chronic Infectious Arthritis		Hypertrophic
Arthritis Deformans		(Osteoarthritis)

These terms are used by different authorities more or less loosely in describing the same conditions. By "infectious arthritis" demonstrable infection of the joint cannot be inferred and this meaning is not intended. If a focus of infection can be demonstrated, which is a probable causative factor in the arthritis, then this term may be used. Chronic non-suppurative arthritis is a descriptive term which commits to nothing. Arthritis deformans, in its common usage is more definite and more descriptive. It is also used by the surgeons, however, to describe the end-results of any single joint inflammation, including even old healed tuberculous lesions of the hip-joint; but in its ordinary medical usage refers to multiple chronic arthritis. As commonly applied these terms may be considered as practically synonymous, inasmuch as the same individual might be classed by different authorities in any one of these groups.

These groups taken together may be divided broadly into an atrophic and a hypertrophic class. Sometimes it is difficult thus to place a case but in general this can usually be done.

Atrophic Form. By atrophy is meant not only atrophy of the bone but also atrophy of all the joint and periarticular structures, atrophy of the skin, and particularly atrophy of certain muscle groups anatomically related to the joint concerned. This condition is *rheumatoid arthritis* and is fairly clear cut in its characteristics.

Starting with acute inflammation of joints, atrophy of the muscles appears with great rapidity. It may even appear before the joint inflammation. The distribution of these lesions is symmetrical. The course is progressive and chronic, interrupted by acute exacer-

bations, also symmetrical. In the early stages inflammation and atrophy are the distinguishing features. In the late stages atrophy and contracture. Ankylosis which may be extreme, is not caused by bony change but by atrophy, contracture, fibrosis and dislocation.

Hypertrophic Form (Osteoarthritis). In this class is included those cases in which bony overgrowth is the distinguishing feature. Ankylosis is the cause of disability. Atrophy is not a marked feature. There may be atrophy from disuse, but this bears no resemblance to the atrophy of the above class. The skin is usually well nourished and subcutaneous fat remains. In place of the emaciation characteristic of the former class many victims of this condition become obese and show little muscle-wasting after years of immobility.

Contrast this condition with the almost total wastage of certain muscle groups seen in the course of a few weeks in rheumatoid arthritis.

II. Septic Joint. By septic joint is meant that condition where the infecting organism is present in the joint and by its direct action on the joint tissues causes the damage. The gonorrheal joint is the commonest example of this. It must not be forgotten that chronic prostatitis or vesiculitis originating in a gonorrheal infection may become a focus of infection for a generalized arthritis of the first class or that a single chronic septic joint may itself be the focus activating a more or less generalized arthritis of a different nature.

III. Trophic Joints. In considering trophic joints, there are certain cases of arthritis where it seems possible to attribute the trouble wholly to trophic disturbance resulting from a recognized lesion of the nervous system and safely to disregard other factors, as in the Charcot joint of tabes or in certain cases of atrophic arthritis occurring in connection with syringomyelia, and possibly in the arthritis which is so frequently seen in connection with Parkinson's disease. Probably many cases of spondylitis are purely trophic in origin.

We shall later take up briefly the profound importance of trophic influences in the development of rheumatoid arthritis (the atrophic form of arthritis deformans). The central nervous lesion, though it certainly exists, is here not demonstrable, and other factors, as focal infection, cannot be disregarded.

IV. Metabolic Joints. Gout is the chief condition concerned in this class of arthritis. It is impossible to disregard the effect of metabolic variations on chronic arthritis in general, as has been well demonstrated by the exhaustive work of Pemberton.² But in gout we appear to have a condition where the products of infection do not play a part in the production of the joint condition and where the toxins concerned are purely the products or results of perverted general metabolic processes or local metabolic failures.

These cases certainly can, in many instances at least, be clearly set outside of the first class.

V. Spondylitis. Spondylitis which often exists without involvement of joints elsewhere, is also frequently seen in connection with generalized arthritis. In rheumatoid or atrophic arthritis, the spondylitis may be hypertrophic in type. Hypertrophic changes may occasionally also be seen in the articulations of the hip and the jaw in cases where the arthritis elsewhere is atrophic; in other words, these articulations situated near the axis of the body may behave differently from the joints more distantly placed.

Chronic villous arthritis is frequently set down as a separate class among the arthritides. This condition may occur in an isolated joint; it is frequently or usually symmetrical in its distribution; muscle atrophy is not marked as in rheumatoid arthritis; atrophy of the cartilages does not occur. There is great swelling and deformity of the joint cavity due to villous overgrowth, ankylosis takes place secondarily with decrease of deformity and the condition becomes an osteoarthritis. This possibly should be classed as an early form of the hypertrophic form. Also, of course, villous overgrowth may take place in isolated joints as a result of trauma or from other causes not related to generalized arthritis.

Syphilitic generalized arthritis is certainly a rarity if it exists at all. It must be borne in mind that in the presence of syphilis, tissue repair is not normal and an acute infectious or inflammatory process which would otherwise promptly clear up may persist simulating a chronic condition. The observed fact that such a condition clears up promptly under anti-luetic treatment does not mean that this condition was syphilitic any more than the commonly seen clearing up of an unresolved pneumonia under mercury and iodid means that the pneumonia was syphilis of the lung. These conditions are often thus interpreted and thus reported.

Fibrositis may simulate arthritis. While joint function is hampered by surrounding fibrous change, this condition is not primarily of the joints. It is probably due to an infection and is possibly related to or identical with rheumatic fever. It seems to occur more frequently and in more aggravated form in Great Britain than in this country—just as rheumatic fever is certainly more widely prevalent and more severe in its fibroid changes in England than it is with us.

Panniculitis. This condition, well described by Stockman,³ does not concern the joints. It may superficially resemble the swelling of a villous arthritis, and this swelling being at times definitely tender, may give rise to pain on motion of the adjacent joint.

The distribution of the lesions in generalized arthritis, and particularly in the atrophic form, rheumatoid arthritis, is so perfectly symmetrical that the control of the distribution most probably in these cases lies in the central nervous system. Symmetry is most

exact not only in the onset of acute inflammation but in the development of contracture. If a joint in a finger is fixed in flexion, the corresponding joint on the other hand is flexed; if another joint is overextended, the corresponding joint of the other hand will be found in overextension; and this symmetry persists not only in type of deformity but in degree.

Where rheumatoid arthritis is not symmetrical, we must look for a nervous cause for the lack of symmetry. In a case seen by one of us the patient had suffered a shell wound of the skull with brain injury and hemiplegia. Following an empyema of the chest, arthritis developed, involving both extremities on the paralyzed side. This arthritis resembled a rheumatoid arthritis in mode of onset. It cleared up after free drainage of the chest. Subsequent attacks were limited to the same side until, with a very severe attack, the hitherto sound side was affected in a perfectly symmetrical distribution but in a milder degree.

Arthritis of either the atrophic or hypertrophic types will be found to be present in a much more severe degree on the paralyzed side in hemiplegias. We recently observed 3 instances of this phenomenon in a single ward at the Philadelphia General Hospital.

With a tendency to generalized arthritis, severe arthritis may develop distal to an injury in a peripheral nerve.

Infection is certainly concerned in many if not most of these cases. It has been satisfactorily demonstrated in so many that its presence as a causative factor may be assumed in a certain number of the other cases. How does this infection operate to produce the joint lesions? In what way can it work to produce the absolute symmetry observed throughout all stages of the disease? The central nervous system must determine the distribution. It is not conceivable that infection of the joints themselves could produce the symmetrical result here seen except under nervous control.

Many nervous conditions, resulting in profound physiological or structural alteration, show little histological change in the cells in which the trouble originates. Adequate and comprehensive microscopical studies of the brain and cord in cases of rheumatoid arthritis are apparently lacking, but the seat of trouble seems to be in the cord. In the hypertrophic form no such definite statement can be made. The sympathetic system seems to play a part in some cases at least, but its importance is probably slight as compared with that of the cord.

It seems probable that the assumed cord lesion is the result of toxic action and not an infection of the cord itself. The latter ought to give a very definite histological picture with which we almost certainly would be familiar.

Treatment. The treatment of chronic arthritis is a subject which has been approached from many angles and unfortunately many reports and discussions are misleading because of a lack of clear

understanding as to the type of disease under discussion. We are confining our discussion to the treatment of rheumatoid arthritis, which we consider to comprise a definite group of cases, showing certain distinguishing characteristics and tendencies. The arthritis of rheumatic fever, as has been said and reiterated, tends to recovery without joint damage. Many cases of arthritis reported as cured by various methods of treatment belong to this class. Metabolic or gouty arthritis demands appropriate treatment and yields well to treatment if joint destruction is not advanced. Chronic villous arthritis is said to respond well to surgical measures, the joints being opened and the hypertrophied synovial villi being resected with benefit (Swett⁴). Septic joints are surgical, though a chronic septic joint may be a focus of infection, causing a generalized arthritis.

Very striking results have been obtained in the treatment of arthritis by foreign protein injected intravenously or by so-called allergic reactions produced by other means. By such methods the acutely inflammatory reaction of rheumatoid arthritis can be promptly reduced or inhibited. Interest in these methods was stimulated by the papers of Miller and Lusk in 1916⁵ and the simultaneous and subsequent publications of Jobling, Peterson,^{6 7} and others. At that time we were treating a number of cases of rheumatic fever and chronic arthritis by intravenous methods in the wards of the Philadelphia General Hospital. We felt that the treatment of rheumatic fever by such drastic methods was unjustifiable as far as it applied to the arthritis, but endeavored to ascertain whether the tendency to the development of carditis in rheumatic fever could be favorably influenced by such treatment.⁸ The importance of arthritis in rheumatic fever is negligible, and the main concern in treatment must be regarding the cardiac condition; but the many papers published at that time gave no hint that this essential phase of the situation was being seriously considered. Attention was focussed on the joint in rheumatic fever, and cases of rheumatic fever and rheumatoid arthritis were not differentiated. We were unable to formulate conclusions regarding the influence of intravenous therapy in the prevention of cardiac complications in rheumatic fever. It can be clearly stated, however, that by intravenous therapy (the so-called allergic reaction or protein shock therapy) the acute inflammatory arthritis of rheumatic fever or the acutely inflammatory phase of rheumatoid arthritis can be checked, inhibited or temporarily put in abeyance.

Intravenous injections are not satisfactory, in that the dosage necessary to produce a given reaction cannot be gauged. A small dose may give a very heavy reaction. Reactions are severe and sometimes alarming. This method is not well adapted to the frequent repetition of doses necessary in chronic arthritis.

In looking for a substitute for intravenous medication we chose Coley's toxin, prepared from cultures of a virulent streptococcus

originally derived from cases of erysipelas combined with *B. prodigiosus*. This preparation had been used for many years in the treatment of sarcoma and experience showed that it was constant in its action and toxicity; the preparation was relatively stable and, injected intramuscularly, it could cause a reaction very similar to the reaction obtained by intravenous injection, but the degree of reaction could be controlled by varying the dose. Experience in treating sarcoma had shown that repeated injections could be given satisfactorily over long periods of time.

We have used Coley's toxin in the treatment of the inflammatory phase of rheumatoid arthritis and have found it satisfactory. Starting the dose at one-quarter of a minim, it is increased by doubling the dose until a reaction occurs. The doses are given at intervals of two to five days at first, preferably about five days. At a five-day interval a given reaction can usually be approximately duplicated by an increase of 50 to 75 per cent over the previous dose.

Focal reaction in the joint with increased soreness may occur after the first two or three injections. This rapidly disappears and a period of amelioration may be expected lasting at first for a day or two and increasing in length after each injection. The interval between injections may be increased to from seven to ten days. As the dose of toxin is increased to about seven or eight minims, a point is reached where little further tolerance is secured and reaction to this dose seems about constant. Local reaction is marked as the dose increases, but focal reactions in the joint cease.

In our experience this method of treatment has been successful in combating the acute inflammatory reaction in the joint. This, of course, is only one phase in the treatment. Contractures, which are responsible for most of the permanent deformity in rheumatoid arthritis, can be overcome surprisingly well by persistent effort. The adaptation of some means of extension by weights is the best means in most cases. In treating contractures which flex the knees, a modified Buck's extension which the patient can attach or release, and having the patient exercise the muscles against this extension, is most satisfactory. A similar apparatus can be hooked to the wrist to extend to the elbow. Baking is useful where fibrosis is a factor and manipulation and massage by a skilled and careful operator are of great service.

It is superfluous to say that the first requisite of treatment is the eradication so far as possible of areas of chronic infection. The most frequently implicated regions seem to be the alveolar process; the next in frequency the tonsil; the prostate and seminal vesicles are certainly responsible for many cases of generalized arthritis. Infection of the accessory sinuses account for a number of cases and infection of the intestinal tract for some. Following the influenza epidemic, intrathoracic infections, such as imperfectly drained empyema of the chest, were frequent causes. Pelvic infec-

tion in the female is probably seldom a cause of arthritis. No dead teeth should be permitted to remain in an arthritic patient; no tonsils should remain if they are suspicious. The clearing up of obvious areas of infection may be sufficient treatment in some cases, but unfortunately is usually not enough, and we never know whether the real source of infection has been attacked.

In treating a case of rheumatoid arthritis, we must have in mind the pathological features causing disability in this condition, atrophy and contracture and fibrosis, and combat these by appropriate measures. Also we must realize that continued inflammation in the joint seems frequently to cause atrophy and contracture. It is not necessary to postulate any specific action on the supposed infection by vaccines, bacterial toxin or intravenously administered substances. The allergic reaction may in itself be accompanied by a general detoxicating effect, and the injection of bacterial toxins may increase the tissue resistance to toxins of this type, so that the joint tissues no longer respond to irritation by an inflammatory reaction.

It is important to recognize rheumatoid arthritis in its early stages and to institute treatment before atrophy and contractures are advanced. This can be done if the characteristics of the disease are appreciated, particularly the symmetrical distribution of inflammation and atrophy.

Conclusions. 1. Rheumatoid arthritis should be clearly distinguished from rheumatic fever before atrophy and contractures have reached advanced stages.

2. Focal infections should be promptly attacked, and mechanical measures employed to overcome contractures. The inflammatory reaction in the joints can be overcome by increasing doses of Coley's toxin administered intramuscularly. The reaction to injections of Coley's toxin resembles the reaction to foreign protein injected intravenously but the dangers and difficulties attendant on intravenous therapy are avoided.

3. In our experience with this method of treatment, extending over several years, the use of Coley's toxin intramuscularly has been successful. We consider it the most important of the various measures employed in treating rheumatoid arthritis.

BIBLIOGRAPHY.

1. McCrae, T.: *A System of Medicine* (Osler and McCrae), 1915.
2. Pemberton, R.: *Metabolism and Treatment of Rheumatoid Arthritis*, *AM. JOUR. MED. SCI.*, 1917, 154, 153.
3. Stockman, R.: *Rheumatism and Arthritis*, Edinburgh, 1920.
4. Swett, P. P.: *Jour. Bone and Joint Surg.*, 1923, 5, 1.
5. Miller, J. W., and Lusk, F. B.: *The Treatment of Arthritis by Intravenous Injections of Foreign Proteins*, *Jour. Am. Med. Assn.*, 1916, 66, 1756.
6. Jobling, J. W., and Petersen, W. F.: *The Non-specific Factors in the Treatment of Disease*, *Jour. Am. Med. Assn.*, 66, 1753.
7. Petersen, W. F.: *Protein Therapy and Non-specific Resistance*; New York, 1922.
8. Torrey, R. G.: *Rheumatic Fever in Tice's Practice of Medicine*, New York, 1920, 2, 589.

REVIEWS.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital; Physician to New England Deaconess Hospital. Third edition. Pp. 784; 30 illustrations. Philadelphia: Lea & Febiger, 1923.

THE name of diabetes is almost synonymous with the name of Joslin. When one thinks of the treatment of this condition and the part played in it by Americans one always thinks of Dr. Joslin. The universal recognition of his ability in the handling and management and treatment of this disease naturally may be considered a satisfactory index of his ability to put into writing what he knows about this disease. The splendid results the first two editions of this book met with are also indicative of the successful reception the book received from the medical profession. Now this present edition, the third, is of particular value and interest because of the discovery of insulin and because of what Dr. Joslin has to say about it. Joslin was one of the first to use the preparation, and certainly is one of the pioneers in the spreading of the clinical knowledge of this preparation, and to him credit is due for many improvements in the management of the patient with this disease. Presumably on account of the importance of this epoch-making discovery of Banting the newest section of the book on insulin is placed first, a hundred pages being devoted to this subject. After this follows the older sections of the book somewhat the same as they appeared previously. There is little that can be criticised in the work of Joslin. He has added much new matter and the material on insulin is up-to-date almost to the last minute before going to press; in that way he has included in the work, one might say, almost the very latest of the experimental and clinical work on insulin. It is interesting to note some of Joslin's methods in the treatment of this disease. He has a tendency to give considerably more protein than is usually given. He has also comparatively little fear of fats, and like most of the workers on diabetes at the present time, he has a tendency to omit the use of alkalies in the treatment of coma. Lastly, and what to the reviewer seems most important, he aims to keep the urine continuously sugar-free, a procedure which varies somewhat in the different diabetic clinics throughout the country.

Some have the patient use insulin only to the point where traces of sugar are found in the first morning specimen of urine. Altogether the book is really a wonderful monograph. The author has succeeded most admirably in getting over to the reader much of the enthusiasm which he has been able to instil in his spoken words.

M.

APPLIED ANATOMY AND KINESIOLOGY. By WILBUR PARDON BOWEN, M.S.; edited by R. TAIT MCKENZIE, B.A., M.D., M.P.E. Third edition. Pp. 352; 217 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

THE understanding of accurate muscular action is most vague even in the minds of otherwise well-trained physicians. A great stimulus to furthering this important knowledge was added by the results of the war. Thousands of cripples and disabled ex-soldiers have been made useful members of society by a reëducation of muscle action. The knowledge of muscle action is just as important to a physician as is the knowledge of nerve function or any other bodily function. This book should help in placing physical education upon the plane that its importance demands and will well continue more and more to demand of the medical advisor. Both the authors are admirably fitted for the intelligent presentation of their subject by virtue of these long experiences in the physical training of hundreds of school and college students.

E.

INDIVIDUAL GYMNASTICS. By LILLIAN CURTIS DREW, Director of Department of Corrective Gymnastics, Central Branch Y. W. C. A., New York. Second edition. Pp. 206; 109 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

PROPERLY applied corrective exercises are exceedingly important in modern life. Such a work is especially welcome in these days of preventive medicine. The value of corrective physical exercise in the developmental periods of years and even in the ordinary individual is a great one. This book not only does this, but indicates the proper relation which gymnastics and other forms of exercise bear to the practice of medicine. The student in this departmental work can be guided intelligently and safely by this little book whose author has had a world of experience in handling individuals as well as groups. It is a book for students of medicine, school teachers, physical instructors and the average individual.

E.

THE FUNDAMENTALS OF BACTERIOLOGY. By CHARLES BRADFIELD MORREY, B.A., M.D., Professor of Bacteriology, Ohio State University. Third edition. Pp. 344; 171 illustrations, 6 plates. Philadelphia and New York: Lea & Febiger, 1923.

ATTENTION is called to a review of the previous edition of this book (AMER. JOUR. MED. SCI., 1921, 162, 750). In this edition several additions and revisions have been made. Most conspicuous of these changes is the substitution of the system recently adopted by the Society of American Bacteriologists for Migula's classification of organisms. This we consider a step in the right direction, although as given here the new classification is not as complete as might be desired. In addition, revisions concerning the standardization of material to a definite H-ion concentration have been included.

ARBOREAL LIFE AND THE EVOLUTION OF THE HUMAN EYE. By E. TREACHER COLLINS, F.R.C.S., Consulting Surgeon to the Royal Ophthalmic Hospital, London. Pp. 108; 25 illustrations, with colored frontispiece. Philadelphia: Lea & Febiger, 1922.

THIS is an extension of the Bowman Lecture, given before the Ophthalmological Society in 1921. By means of comparative anatomy and comparative histology the author succeeds in delineating the structure of the human eye in a most interesting way. He adopts an evolutionary point of view and shows how the human eye has become adapted to its present uses. For comparison he describes the structure of the eyes of a number of other species, and points out their various adaptations. Thus we have panoramic, binocular and stereoscopic types of vision. In each of these types the parts of the eyes show definite structural variations, which can be readily recognized, some with and some without the microscope. Thus the relative size of the cornea and the size and shape of the pupil, as well as the size and shape of the lens, vary greatly and the variations are readily seen. The differences in the ciliary body and in the retina require study with the microscope to be determined. The book will appeal to all interested in the eye and vision, clinicians zoölogists and psychologists as well.

THE PHYSIOLOGY OF TWINNING. By H. H. NEWMAN, Professor of Zoölogy, University of Chicago. Pp. 230; 71 illustrations. Chicago: The University of Chicago Press, 1923.

THE author's previous book on this subject, *The Biology of Twins*, published six years ago, was largely morphological in char-

acter and dealt with mammals only. In the present volume the scope is extended to include the theories relating to the causes of twins and to the influences of twins upon each other, as well as to describe all the known types of complete or partial one-egg twinning in the animal kingdom. Separate chapters are devoted to twinning in starfishes, earthworms, fishes, birds, armadillos and other vertebrates. Of the several chapters describing human twinning, perhaps the most interesting is the one on the developmental hazards of human twins. As to the interpretation of double monsters, the author believes that they are the products of incompletely divided single embryos and not the fusion of two embryonic axes. The book is an important contribution to this special field. A.

PROTISTS AND DISEASE. By J. JACKSON CLARKE, F.R.S.C., Senior Surgeon to the Hampstead and Northwest London Hospital. Pp. 229; 61 illustrations. New York: William Wood & Co., 1923.

THE search for the causal organisms of disease leads the student into many regions of biology. The author of this work, at once a surgeon and a pathologist by vocation, has paid attention for many years to the protists, or group comprising the lowest animals and plants. In this, his sixth volume on the subject, he discusses a number of these organisms and their relation to some of the more serious diseases of the human body. A.

RHUS DERMATITIS. By JAMES B. MCNAIR, M.D. Pp. 300; 15 illustrations and 3 plates. Chicago: University of Chicago Press, 1923.

MCNAIR's monograph is of the welcome sort in which the research has been deliberately planned, recorded in detail and supplemented by an analysis of the literature. He begins with the bionomics of the several poison ivy species, and thereafter covers the anatomy, modes of transmission of the toxic resin (not fat) from plant to person, the chemistry of the poisonous principle and finally the pathology, including immunity, differential diagnosis and treatment of the disease. Most of these sections have appeared in the literature from time to time, but while the book is thus largely a collection of reprints the work was so planned that there is a perfectly satisfactory thread of continuity between the sections as they now appear in book form.

Some of the points which will command the attention of the medical man are as follows: The active toxic agent is a non-volatile resin which McNair calls lobinol. Its formula is unknown, but it is a probable phenol. There have been a few cases of fatal internal ivy poisoning. Chewing of leaves (to induce immunity) has produced perianal dermatitis, internal poisoning and one death. In 49 bed-fast cases, 35 per cent showed albuminuria, and one patient developed acute nephritis. Leukocyte counts ranged from 14,000 to 31,600. There was no eosinophilia. Immunity is only relative, apply sufficient poison and the so-called immunes will react. Ferric chloride in aqueous 5 per cent solution is recommended as the rational antidote.

Thirty-five pages of abstracts and a bibliography of sixty-seven pages make this book a mine of information.

Viewing McNair's book on the whole, the reviewer is impressed in the wise that although the subject of rhus dermatitis has thus come to appear exhaustively in book-form it must not be presumed that it itself has been exhausted, and that we can relax in our inquiries into the subject. This must be avoided. Rather has McNair established a fine nucleus around which new findings ought to accumulate, and these are still sorely needed in respect to the pathology and treatment of the disease.

W.

A TEXT-BOOK OF CHEMISTRY FOR NURSES. By FREDUS N. PETERS, A.M., PH.D., Professor of Organic Chemistry, Hahnemann Medical College, Kansas City. Second edition. Pp. 302; 39 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS manual deals with the subject in a simple rather than an elementary style. Wherever possible the practical aspects of chemistry and the relation of the bases, acids and salts to medicine have been discussed. Of value to the nurse will be the various tables, the chapter on common poisons and the compilations of scientific and common names and terms for chemicals in the appendix and glossary.

W.

OBSTETRICS FOR NURSES. By CHARLES B. REED, M.D., Obstetrician to Wesley Memorial Hospital, Chicago. Second edition. Pp. 300; 144 illustrations, including two color plates. St. Louis: C. V. Mosby Company, 1923.

THAT Dr. Reed's book has necessitated a second edition would seem to reflect that his method of presentation of this subject had

been approved in a wide degree. The one criticism that might be offered to this book, which is not a manual on nursing in obstetrics, but, as its title says, obstetrics for nurses, is that it is too full, too advanced, too technical, as for instance when he offers to nurses the indications and contraindications for using pituitrin. For the most part the field of obstetrics is well covered, and much of the text has been revised.

W.

DISCOURS DE LA NATURE DE L'AIR; DE LA VEGETATIONS DES PLANTES. By EDMÉ MARIOTTE (1620 ca.-1684). Reprinted. Paris: Gauthier-Villars, 1923.

NOT only does the present rapid growth of scientific discoveries tend to obscure the work of the pioneers in science, but also their chef-d'oeuvres are as a rule extremely expensive and scarce. For this reason, Gauthier-Villars are publishing a series of "Maitres de la Pensée Scientifique," under the editorship of Maurice Solovine, of which series the present volume is the sixteenth. Although all branches of science are represented, the cultured physician will find many interesting contacts in accurate editions of the most important works of Huygens, Lavoisier, Spallanzani, Ampère, La Place and Pascal at the ridiculously low price of three to four francs a volume.

K.

THE ACTION OF ALCOHOL ON MAN. By ERNEST H. STARLING, Foulerton Professor of Physiology, University College, London. Pp. 291; 12 illustrations. London: Longmans, Greene & Co., 1923.

DR. STARLING, who has described the action of alcohol on man from a purely scientific physiological standpoint in the light of our most recent knowledge, comes to the conclusion that "in moderation it is difficult to appreciate any harmful effects from its use, whereas when temperance is abandoned and alcohol is used immoderately its effects are evil and fraught with disaster to the individual and damage to the community." The book also includes three separate essays, one on "Alcohol as a Medicine" by Dr. Robert Hutchinson; one by Sir Frederick W. Mott on "Alcohol and its Relation to Problems in Mental Disorders," and one by Dr. Raymond Pearl on "Alcohol and Mortality." Mott concludes that alcohol plays a relatively unimportant part in the production of certified insanity; and Pearl states that while the moderate consumption of alcoholic beverages does not sensibly shorten the mean duration of life nor increase the rate of mortality as compared

with that of total abstainers, still its excessive use definitely diminishes the mean duration of life and increases the rate of mortality. The evidence as well as the opinions of all these writers would seem to indicate that the abolition of all alcoholic drinks in so-called civilized society is a mistake and contrary to the permanent interest of the race. The book lays stress on all the benefits which the present generation may obtain by the use of alcohol. Though Stockard's experimental studies of the influence of alcohol on the given cells and his analysis of the hereditary transmission of degeneracy and deformity by the descendants of alcoholized mammals, are mentioned, the benefits that might accrue to the race in the future, as shown by Stockard, by the elimination of the weak, the unfit, and the defective, might have been further dilated upon as the most important argument for the repeal of the eighteenth amendment of our Constitution. O.

THE NEW DIETETICS. By JOHN HARVEY KELLOGG, M.D., LL.D., F.A.C.S., Superintendent of Battle Creek Sanitarium, President of Battle Creek College. Second edition. Pp. 1021; 18 illustrations. Battle Creek: The Modern Medicine Publishing Company, 1923.

THIS is an interesting and stimulating book which the reviewer recommends to physicians. It contains, however, too much unproven opinion presented as fact, and too many examples of "partisan inference" to make it a safe guide for "the trained nurse, the intelligent housewife, as well as the professional dietitian"—all of whom the author includes in his presentation. The author is a crusader against what he believes to be one of the greatest ills that civilized man is subject to—viz., colonic stasis and autointoxication from high protein diet and other "unbiological practices." F-H.

DIAGNOSTIC METHODS. By HERBERT THOMAS BROOKS, A.B., M.D., F.A.C.P., Professor of Clinical Medicine, College of Medical Evangelists. Fourth edition. Pp. 109, 52 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS manual represents an attempt to epitomize the usual diagnostic methods employed in the study of patients. The author's ideals of accuracy and completeness have naturally come in conflict with the limitations of allotted space. The author wisely advises that in addition some extensive work on Clinical Diagnosis be used as a reference book. F-H.

INFECTION, IMMUNITY AND BIOLOGIC THERAPY. By JOHN A. KOLMER, M.D., Professor of Pathology and Bacteriology in the Graduate School of Medicine, University of Pennsylvania, and Member of the Research Institute of Cutaneous Medicine, Philadelphia. Third edition. Pp. 1210; 202 illustrations. Philadelphia: W. B. Saunders Company, 1923.

ONE might say in going over the third edition of Kolmer's textbook on Infection, Immunity and Biologic Therapy that it is almost a new book. This is due to two factors: First, that a complete revision was necessary as the previous two editions, appearing as they did before the war, were out of date on account of the rapid advances in this branch of medicine, while the second factor is the result of the large amount of new material which the author has seen fit to add to the work. The book is divided into five parts. Part 1 deals with general immunological technic, the second part with principles of infection, the third with principles of immunity, the fourth with clinical allergy and biological therapy and the last with a series of experiments arranged for the student. Discussing seriatim the several parts it may be said that Part 1 is a general description of the methods employed in preparing and making sera as well as the principles of collecting body fluids. Part 2 is a discussion of the general principles of infection. Part 3, the longest section of the book and probably the most important to the student, contains a most broad and at the same time a detailed discussion of immunity and immunological technic. In this section, of course, the greatest value is to be placed on a very thorough, minute discussion of the Wassermann complement-fixation test, particularly from the standpoint of the modifications which the author has introduced into this procedure. Part 4 is the section which should be of most value to the practitioner of medicine, as it contains a full exposition of allergy and the treatment of the condition as well as chapters on the use of sera, non-specific protein therapy, vaccines, blood transfusion, and so on. The last part is a series of experiments designed entirely for the laboratory instruction of the student. The work is a most splendid, first-hand presentation of the subject. It is not a compilation in any sense, as are so many books, but represents for the most part the result of the personal studies of a most indefatigable worker. There is little to criticise about the work. One might take exception at times to the lack of standardization in nomenclature. For example, in the classification of allergy, the terms that are employed vary considerably with different authors and Kolmer has seen fit to still further confuse the subject by adding a classification of his own. Of course, the obvious excuse is that the subject is so new that it has not had time to be standardized.

M.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Intravascular Injection of Iodized Oil.—SICARD and FORESTIER (*Compt. rend. Soc. de biol.*, 1923, 88, 1200), making use of the great opacity to roentgen-rays and the remarkable tolerance of the organism to iodized oil (lipiodol), have succeeded in studying in man and animals many cavities and spaces until now unexplored. The subarachnoid and epidural spaces, the broncho-pulmonary tree, abscess cavities, etc., have been successfully explored without harm or danger. Their most recent work has been concerned with injections of the oil into different vascular trunks of the dog, watching by means of the fluoroscope screen and serial roentgenographs its distribution and passage through capillary beds. "Injection of 5 cc of the lipiodol into the femoral vein of a 5-kg. dog caused no respiratory or cardiac embarrassment, provided two to three minutes were taken for the injection. One may see under the screen white oily drops issuing from the needle and carried by the blood current with progressive acceleration to the iliac vein and then to the heart. Arriving in the right cavity of the heart, the drops are pulverized by the ventricular contraction, which projects the droplets with great speed into the pulmonary artery. After penetrating very nearly uniformly into the two branches of this artery, the droplets are quickly arrested in the capillary network of the different parts of the lung. The total time of travel from the femoral vein to the pulmonary stoppage was about six to seven seconds." These droplets disappear from the capillaries in ten to twelve minutes. Injection of 8 cc of the oil into the portal vein showed a very sluggish movement of the blood current, two to three minutes being required for even the larger branches in the liver to be penetrated. After one and a half hours all the oil appears still to be in the hepatic capil-

lary network. When arteries such as the femoral or carotid receive the injection there is very rapid distribution of the oil, with its appearance in the venous return within two minutes. No circulatory or other disturbances are caused in the animal unless the injection be made too rapidly. This work opens an interesting field for the study of the permeability of different capillary beds to oils and of the topography of the vessels in the intact organism. Also abnormal states of the circulatory apparatus may be directly studied.

Sickle-cell Anemia.—J. G. HUCK (*Bull. Johns Hopkins Hosp.*, 1923, 34, 335) reports observations upon sickle-cell anemia, based on a study of 14 cases. Hitherto, only 4 cases have been recorded, the first by J. B. Herrick in 1910. The cases studied by the author occurred in three generations of two families. As a result of his observations, he concludes that sickle-cell anemia is "a hereditary disease, transmitted by and occurring in both males and females with equal frequency, in which the red cells of the blood acquire a characteristic sickle or crescent shape *in vitro*. The disease is characterized by certain typical clinical symptoms, especially those of anemia and leg ulcer." The disease has been observed only in negroes. No infective etiological agent has been discovered. No postmortem findings have been reported. The blood shows an anemia, the red cells varying between 1,500,000 and 4,000,000, the hemoglobin between 30 per cent and 63 per cent. The color index is usually normal or high. There is a slight increase in the white count (10,000 to 20,000) with increase in the percentage of polymorphonuclear neutrophils. A few myelocytes, chiefly neutrophilic, may be observed. Cells of the large mononuclear variety are seen at times, phagocytizing red cells. "The poikilocytosis consists mostly of crescent or sickle-shaped cells with an occasional oat-shaped cell." Basophilic granulation and polychromatophilia are observed. Nucleated reds (normoblasts, intermediates and megaloblasts) may be found, chiefly normoblasts. No Cabot rings or Howel bodies have been observed. "Fresh wet preparations of the blood, that have been sealed with petroleum jelly, reveal a most interesting phenomenon. Immediately on examination of the preparation one finds only a few of the erythrocytes having a crescent or sickle shape, but after from six to twenty-four hours, from 25 per cent to 100 per cent of the cells, according to the severity of the disease, acquire bizarre forms." The cells show a slight decrease in resistance to hypotonic salt solutions. Reticulated cells, as demonstrated by vital staining, are greatly increased, even to 35 per cent. The bilirubin content of the serum is high. In the severe forms of the disease, the prognosis is unfavorable on account of a susceptibility to acute intercurrent infections, especially pneumonia and tonsillitis. Treatment is symptomatic.

A Warning Against the Use of Arsphenamine in the Treatment of Syphilis in a Hemophiliac.—ROSENBLUM (*Jour. Lab. and Clin. Med.*, 1923, 9, 57) reports the case of a colored man who had been bleeding from a tooth socket for two weeks following extraction of the tooth. His hemoglobin was 40 per cent and red cells 2,300,000. There was a history of an initial lesion fifteen years previous and the Wassermann was ++++. After attempting to stop the hemorrhage by transfu-

sion and the injection of horse serum, 0.6 gm. arsphenamine was given. Within an hour after this injection all his gums began bleeding alarmingly. This loss of blood was partly checked by adrenalin compresses but in spite of three transfusions and the use of coagulose, horse serum, etc., the bleeding continued until his death two weeks later. From this experience, and on the basis of experimental findings pointing to an interference with normal clotting by arsphenamine, Rosenbloom feels that the use of this drug is contraindicated in hemophilia.

Spinal Subarachnoid Block.—AYER (*Arch. Neurol. and Psychiat.*, 1923, 10, 420) describes a method which consists of manometrical study of fluid by double puncture and comparison of fluids at different loci. For the hydrodynamical studies, the points of puncture are above and below the obstruction. The protein content of the fluid from below the point of obstruction is increased. Most of the fluids from below the obstruction are colorless. Fifty-three cases of block studies, 41 complete. Block was caused by tumors, by vertebral disease and dislocation and by meningitis. Below point of obstruction, pressure of the spinal fluid is either not affected or only slightly affected by such manœuvres as jugular compression. Of 104 cases, in which no block, complete or partial, could be demonstrated, 3 proved later to have compression of the cord. Two of these, however, showed marked increase of protein below the tumors. It would seem that the demonstration of block and the increased protein content of the fluid from the lower needle are valuable indices as to the permeability of the spinal subarachnoid space.

The Size of the Heart in Pneumonia.—LEVY (*Arch. Int. Med.*, 1923, 32, 359) made teleoroentgenograms of 21 cases of lobar pneumonia and 8 cases of bronchopneumonia. Three normal young men and 1 patient with fever, due to pulmonary tuberculosis, acted as controls. Care was taken to secure proper alignment, and a simple geometrical method was used to complete the outlines of the cardiac shadow. The area so delineated was measured with a plain meter. The controls showed very little change in transverse or long diameters or in surface area. A variation of 1 cm. or more in one of the diameters, or of 10 sq. cm. or more in area was regarded as significant. Of the 21 cases of lobar pneumonia, 13 showed an increase in the size of the heart. Eleven of the patients were given digitalis; 10 were not. Of the 11 patients, 8 (72.7 per cent) showed cardiac enlargement; of the 10, 50 per cent showed cardiac enlargement. Eight cases of bronchopneumonia were observed, 2 showing a change in the size of cardiac silhouette.

The Treatment of Syphilis with Bismuth.—McCAFFERTY (*Arch. Dermat. and Syph.*, 1923, 8, 469) reports the treatment of 25 cases of syphilis, in all stages, by bismuth. Potassium and sodium tartrobismuthate is used. Two cc, or 20 cg. of active bismuth, suspended in oil, is given intramuscularly every four days. Twelve to 16 such injections constitute a course. There is evidence to show that this agent is as effective as arsphenamine in treating primary and secondary manifestations, although its action may be slower. Bismuth would seem

to be very useful in treating "Wassermann-fast" individuals, as well as those having an idiosyncrasy towards arsenic. Nothing definite can be said about its action in neurosyphilis. Pigmentation of the gums and stomatitis may occur. Local pain at site of injection is said to be negligible. A good working bibliography is added to this article.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Further Observations on the Blood-pressure in Cases of Urinary Obstruction.—O'CONNOR (*Jour. Urol.*, 1923, 10, 135) states that complete drainage of the bladder in patients suffering from urinary retention is attended by a marked fall of systolic blood-pressure during the first forty-eight hours. During this period the renal function is diminished as shown by the phenolsulphonephthalein test and the quantitative determination of urea in the blood. If, however, the retained urine is gradually evacuated, the decrease in pulse pressure will be less marked, and the renal function only slightly diminished. Before instituting permanent drainage all patients in the preuremic or dehydrated condition should be amply supplied with fluid. This can be quickly and safely accomplished by intravenous injection of glucose solution. If satisfactory drainage of the bladder is continued, the blood-pressure is gradually maintained at a definite non-fluctuating level. Patients prepared for operation by waiting until this fixed blood-pressure level has been established have shown a very insignificant postoperative decrease in blood-pressure, especially when glucose solution is given intravenously, both before and after operation. Obstruction in the course of the urinary tract must be considered in many instances as a cause *per se* of high systemic blood-pressure. This may be equally true even though the residual urine is small in amount. In papillary epitheliomata hematuria is usually present being intermittent in character. Pain is noted in half of the cases. Pyelography reveals deformity of the pelvic outline in almost every case. This type of growth is seldom seen in patients under forty years of age. Metastases in bladder and ureter are common.

Operations for Inguinal Hernia Under Local Anesthesia.—BLOODGOOD (*Am. Jour. Surg.*, 1923, 37, 185) describes the full technic of local anesthesia with one-quarter of 1 per cent of novacaine. He likewise gives detailed account of his technic for inguinal hernia. The author states that both Bassini and Halstead laid great stress upon

the transplantation of the cord. Follow up studies showed that the transplantation of the cord was not an essential feature in the operation for inguinal hernia for the chief cause of recurrence was the weakness or obliteration of the conjoined tendon and this was not in the position of the transplanted cord. Other recurrences, a very small number, could be explained by the large size of the cord, and in this group the recurrence occurred alongside of the cord. In a small percentage of the cases, the recurrence could be more easily explained by faulty suture or extreme weakness of the tissues available for suture. Healing of the wound is not as perfect in the hands of surgeons, not deeply experienced in local anesthesia. But the breakdown of the wound is usually confined to the skin and fat, and seems to have no influence on the result.

Vasostomy for Seminal Vesiculitis.—KIDD (*Lancet*, 1923, 2, 213) says that a seminal vesicle infected with gonococcus or *B. coli* or other germ can remain blocked and full of the infecting agent for many years. The victim may suffer from relapsing fever and rigors from relapsing urethral discharges, from arthritis or iritis, from impotence and sterility, and from neurasthenia. In some cases the neurasthenia is so severe as almost to amount to a psychosis. The author definitely states that all these troubles except the irites can be cured by vasostomy. He feels that this procedure, which he describes at length should be used in all cases of chronic relapsing gonorrhea (or *B. coli* or streptococcal vesiculitis) in which there is evidence of a thickened closed vesicle or vesicles and in which four or six months' consecutive and careful treatment by massage, urethroscopy and so forth has failed to produce a cure. Vasostomy is also indicated for cases of chronic arthritis, with chronic relapsing epididymitis that do not yield to such treatment. It should also be used for cases of relapsing attacks of fever, rigors, pyuria, epididymitis caused by the colon bacillus or other germs such as streptococci. In the final group, he states that it should be used for many cases of severe arthritis in the early stages. Belfield has reported 83 cases of posterior urethritis, with acute vesiculitis and arthritis, where immediate amelioration has been obtained by vasostomy.

Secondary Signs of Gall-bladder Pathology.—LEONARD (*Am. Jour. Roentgenol.*, 1923, 10, 521) says that roentgen-ray evidences of gall-bladder pathology is divided into two classes—direct and indirect: In the first are put the demonstrable stones and visible gall-bladders. In the indirect class are put the demonstrable changes produced by gall-bladder disease. This latter class is by far the most important, in it are included the pressure deformities, chiefly by the duodenum; the changes caused by adhesions including fixation of adjacent organs by adhesions, and deformities in outline of adjacent organs from adhesions; the field of gastric reflex (typical gall-bladder spasm); lastly the ampulla of Vater, when made visible by barium has, in the author's experience, been associated with some type of past or present gall-bladder disease.

A Conservative Treatment of Carbuncles.—LEWIS (*Ann. Surg.*, 1923, 78, 649) says that only 3 cases of carbuncles treated by roentgen-ray

were found in the literature. Sixteen unselected cases of carbuncles treated by roentgen-ray are here reported. Only 2 of these 16 cases required operative treatment. Diameters of induration increased more than 2 cm. after roentgen-ray treatment in only 2 cases, and in 1 of these it was probably due to a too narrow protecting of the field of the roentgen-ray in giving the treatment. Sloughing and suppuration, and the skin sinuses through which this took place were surprisingly slight in the small and moderate sized carbuncles. The very large carbuncles resolved into enormous, sharply demarcated abscesses, which drained satisfactorily through the sinuses formed by sloughing of the overlying skin. Pain was relieved following the roentgen-ray treatment in the majority of cases. The duration of small and moderate sized carbuncles seemed much shorter with roentgen-ray therapy than under operative treatment. The duration of the very large carbuncles seemed about the same with roentgen-ray or operative treatment. Cosmetic results were superior with roentgen-ray. Great preference for the roentgen-ray treatment was expressed by patients with experience in other forms of treatment. The method seems relatively safe. The comparative absence of traumatism as compared with operation seems a protective measure of importance.

The Surgical Management of Gall-bladder Disease.—FINKENHEIM (*Zentralb. f. Chir.*, 1923, 27, 1050) classified operated gall-bladder cases as chronic cholecystitis, acute cholecystitis, chronic cholecystitis with acute exacerbation. The last group contained approximately 40 per cent of a *large series* of 670 cases. Sixteen cases showed perforation, half rupturing into the peritoneal cavity, and half were walled off by strong surrounding adhesions and inflammatory processes. A second group is given of 74 cases, in 57 of which were found at operation the marks of definite processes of inflammation, but with no stones. In 17 neither inflammatory processes nor stones were found. A third class contains the empyema group, 115 in all, 98 of which had stones and pus, while 17 exhibited pus without stones. A fourth grouping contained 11 cases of hydrops. The fifth set embraces all grades of inflammatory interference in the common duct. Stones were present in 100 of 136 cases. The sixth group comprised 10 cases of gall-bladder ileus; while the seventh place in the classification comprised 41 cases of carcinoma. Complications or associated diseases were present in 32 cases. In 22 instances cholelithiasis was primary, appendicitis, ulcer of duodenum, and other diseases being secondary. In 10 cases the associated pathology was primary, and the gall stones secondary. Secondary operation occurred in 37 cases. The author finds the solution of operative procedure simple: Cholecystectomy is the routine procedure for cases with pathology localized in the gall-bladder, while cholecystostomy is reserved for those cases unable to stand general anesthesia for a long period, with disease of heart and lungs. The routine procedure for operations on the common duct was choledochostomy—choledochotomy with suture was performed in 30 cases. For mortality, 16 deaths occurred from pulmonary causes, 18 from cardiac failures, 8 from clotting deficiencies in the blood, peritonitis with perforation 10 cases, peritonitis without perforation 11, collapse and inanition 24, septicemia 2, and cachexia 2.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK.

Medical Methods of Controlling Hemorrhage.—KAYSER (*Med. Klin.*, July, 1923) writes that many methods such as hypertonic salt solution, organ extracts, coagulen, serum, peptone, etc., have been employed as aids to control hemorrhage, but as yet no one remedy has proved infallible. In addition, the surgeon has often to resort to medical means in cases of postoperative hemorrhage. Nonnenbruch and Szyska have investigated euphyllin and ethylenediamin as a means to increase blood coagulation. Euphyllin, one of the purin bodies, contains about 80 per cent theophyllin and about 20 per cent ethylenediamin. Euphyllin is employed as a diuretic and heart stimulant. They found that it increased the coagulation of the blood when used subcutaneously, intramuscularly or intravenously, this reaction reaching its highest point in four to five hours after injection, and the effect lasting up to twenty hours. Other workers found that the active principle of euphyllin in this reaction is ethylenediamin. Investigations showed that the latter used alone gives like results. Nonnenbruch believes that this substance acts on the blood indirectly, causing a mobilization of the substance in the blood that brings about coagulation. The author of this article thought of trying something combined with ethylenediamin to enhance the reaction of coagulation of the blood. The effect and action of calcium in the blood is well known. He took ethylenediamin acetate and a calcium salt and obtained a compound, crystalline in character and soluble in water, which he calls hämosistan. Using rabbits he found that 1 cc of a 10 per cent solution given intravenously resulted in a marked increase in the coagulation of the blood, reducing the time on the average from fifteen to five minutes. The peak of the reaction is reached in an hour and the effect is manifest up to forty-eight hours. No symptoms are evidenced. Hämosistan is given intravenously as other methods of administration are painful. It has been used in man in various clinics in Berlin, with results that are better than in the animal experiments. Ten cc of a 2 per cent solution is the optimum dose. It has been employed in hemorrhages of all kinds and may be secured in ampules.

The Treatment of Vincent's Angina with Trypaflavin.—In 14 cases of Vincent's angina, BUSCHMANN (*Deutsch. med. Wchnschr.*, 1923, 19, 617) used trypaflavin, painting the throat each day for three or four days and having the patients gargle with a solution of trypaflavin. He claims that they have cleared up in from three to seven days.

Studies of Turpentine.—KLINGMÜLLER (*Deutsch. med. Wchnschr.*, 1923, 21, 669) advocates the use of turpentine in those cases in which non-specific therapy is used for temperature reactions. He uses a special

preparation called olobintin, which is a preparation of turpentine in oil. This injection causes the formation of a sterile abscess which is open when indicated.

The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis.—LOAKWOOD and CHAMBERLIN (*Arch. Int. Med.*, 1923, 32, 74) report the effects on gastric function of the administration of a standard dose of four commonly used alkalis. The antacids were all given with the Ewald meal and comparison made with control curves in 26 cases. Neither sodium bicarbonate, calcium carbonate, magnesium oxide or bismuth subnitrate seemed to affect the evacuation time of the stomach. This does not support Cannon's conception of the acid control of the pylorus. The phenomenon of bile regurgitation was also unaffected. The average free and total acidity was lower after the administration of the alkali in all observations on calcium carbonate and magnesium oxide. In rather less than one-fourth of the sodium bicarbonate tests it was actually higher. The average acidity was unaffected by bismuth subnitrate. After sodium bicarbonate the acidity rose to a higher point than in controls in about one-half the cases; after calcium carbonate, in one-fourth and after magnesium oxide in one-fifth of the cases. After bismuth, the acidity attained a higher point in only 2 of the 7 cases. The results with the different alkalis are not strictly comparable since the neutralizing power of soda is only one-half that of calcium carbonate and one-fourth that of magnesium oxide. It is possible that with a dose of soda equal in strength to the dose of calcium or magnesium, the acid rebound would have been less in evidence. On the other hand, the liberation of carbon dioxide when soda is administered may have acted as a direct stimulant.

The Pathogenicity and Treatment of Flagellate Dysentery.—According to WHITTINGHAM (*Brit. Med. Jour.*, May, 1923, p. 1799) flagellate dysentery is a pathogenical condition which if allowed to persist will eventually undermine the health of the patient and cause neurasthenia, and he states that all cases of recurrent diarrhea or neurasthenia for which no cause can be found and in which flagellates have been detected in the stools should have a course of treatment. Certain cases are simply carriers, and these are a great source of danger as they may infect others. He says that flagellate dysentery may be cured in at least 50 per cent of the cases by the treatment he advocates. The patient is put to bed and kept upon as light a diet as possible for three days. At the same time sodium bicarbonate is given thrice daily in 15 grain doses, to clear away any mucus coating the internal surface of the gut. To further clear the intestines, 3 grains of calomel are given at bedtime on the third day, followed by magnesium sulphate the next morning. When the bowels have moved, thymol in three doses of 30 grains each is given at hour intervals. At midday another dose of magnesium sulphate is given to remove excess of thymol and lessen the danger of poisoning. No food is permitted until after the thymol treatment is completed. At bedtime emetine bismuthous iodide powder is given for ten consecutive days: 1 grain the first night, 2 grains the second, thereafter 3 grains until a total of 33 grains have

been taken. During the fortnight following the thymol treatment high lavage of the colon is performed on alternate mornings with a solution of quinine in water. After the course of emetine treatment the stools were examined daily for at least three weeks; if the findings were negative, monthly examinations were made for four months. Relapses were treated in the same manner. In only a few cases was a third treatment necessary. Cases which did not respond to this treatment, were considered as practically incurable.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Acidified Whole Milk as a Routine Infant Food.—MARRIOTT and DAVIDSON (*Jour. Am. Med. Assn.*, 1923, 81, 2007) give the method of preparing this modification of cow's milk. A good grade of cow's milk is first sterilized by boiling for five minutes. The milk is then cooled and the scum removed. When thoroughly cooled, lactic acid is dropped in slowly, while the milk is gently stirred. Lactic acid (U.S.P.) is used and the amount required is 1 dram to each pint of milk. This is added a drop at a time from a medicine dropper. If the milk is warm when the lactic acid is added, or if the acid is run in too rapidly, large lumps of curds will separate. When properly prepared a smooth, homogenous preparation should result. The concentration of acid is the same as that occurring in ordinary buttermilk and the taste and general physical properties are much the same. In using lactic acid milk for infant feeding dilution is usually not necessary, as the amount an infant would ordinarily take at a feeding is not in excess of the digestive capacity. Carbohydrate should be added to lactic acid milk, as the amount of sugar present is insufficient for the needs of the average infant. The authors recommend commercial corn syrup sold under the name of Karo. This syrup contains a relatively high amount of the difficultly fermentable dextrin, and can consequently be added to the lactic acid milk in large amounts without the danger of producing diarrhea. The amount of syrup usually added to the day's feedings is 1 ounce for infants up to two weeks of age, and from 1½ to 2 ounces for the older infants. In preparing the formulas, the syrup is stirred into the lactic acid milk until it is thoroughly mixed. In cold weather the syrup may be mixed with an equal volume of warm water to facilitate the mixing. Of 142 infants fed in this way, 78 or 55 per cent were suffering from infections during the period of observation. These included otitis media, pneumonia, pyelitis, meningitis, pulmonary tuberculosis, bacillary dysentery, and osteomyelitis. Included in this series were also cases of congenital syphilis, pyloric stenosis, congenital malformations of the heart and spina bifida. These are the usual run of cases seen in the infant ward of any large hospital. The ages of the infants varied from two days to one year. A large proportion of the infants were underweight. Six premature infants are

included in this series. More than half of the babies were under three months of age. The number of days that the formulas were fed varied seven to one hundred and twenty. The average was twenty-two days. The average number of calories fed was 153 per kilogram of body weight. Seventeen of the infants received more than 200 calories per kilogram of body weight. For the entire series the average daily gain in weight was 28 gm. Gain in weight is not the only criterion of the suitability of the diet. The infants in this series rarely developed diarrhea or vomiting. None died as the result of gastro-intestinal disturbance attributable to overfeeding. The mortality of the athreptic infants in the hospital has fallen from 78 per cent in 1919 to 26 per cent during the past year.

Recurring Cardiac Infections in Children with Chronic Valvular Disease.—SMITH and STULIK (*Am. Jour. Dis. Child.*, 1923, 26, 396) observed 80 children during a period of three years. Twenty-one or 26 per cent had frequent periods of slight fever ranging from 99.2° to 100.4° F. In 16 of these, the diagnosis of an active cardiac infection was made. In 7 cases, the diagnosis was based on the finding of a conduction defect of the auriculo-ventricular bundle. Two had premature contractions during periods of fever, one of whom later had definite cardiac dilatation. In the remaining 7, the conclusions concerning the presence of a cardiac infection were based on definite changes in the physical findings of the heart, such as the appearance of a new murmur, a pericardial rub or demonstrable cardiac dilatation. The rate of progression of the cardiac disease was much more rapid and the incidence of severely damaged hearts far greater in the 21 children with recurring periods of temperature than in the remaining 59. The diagnosis of active cardiac infection in children with chronic valvular disease may be difficult, and several weeks may elapse before definite manifestations appear. The electrocardiograph may enable a diagnosis being made earlier in the course of the infection. It was pointed out that one of the difficult problems of the physician in treating children with chronic valvular disease is preventing the condition from progressing. It was suggested that the difficulty might in a measure be overcome by the education of the public, the early elimination of all possible oral and nasopharyngeal infections, and the establishment of convalescent homes.

Chronic Ulcerative Colitis in Childhood.—HELMHOLZ (*Am. Jour. Dis. Child.*, 1923, 26, 418) reports 5 cases. He comments that, so far as is known, there is no definite etiological factor in this condition. It may be the result of a variety of infections, pyogenic, dysenteric, amoebic, or tuberculous; but wherever a specific cause can be demonstrated, the condition is usually not chronic ulcerative colitis. In none of the cases reported was it possible to demonstrate the presence of any of these infections. In only 2 cases were there other cases of dysentery in the community, and in these two epidemics, all other patients recovered uneventfully in the course of a few weeks. In 1 case the patient had his first attack following scarlet fever complicated by otitis media. In 4 of the 5 cases, the colitis started acutely with a bloody diarrhea. In only one instance was the condition chronic and without diarrhea. The onset was so lacking in symptoms that the small

amount of bloody mucus that the mother noticed on the underclothing was interpreted as the beginning of menstruation. When it continued for a few weeks medical advice was sought. In spite of the treatment the girl became gradually worse. Dysentery did not develop until several weeks later, following an acute bronchopneumonia. As was seen in 1 case the ulceration begins in the lower portion of the bowel, and in the course of the illness the entire colon is involved. In 2 cases that came to necropsy there were ulcerations in the ileum, but this involvement is rare. On proctoscopic examination, the ulcers are usually most marked in the rectum and lower sigmoid, and in the early cases become less numerous in the sigmoid. The colon is usually thickened, the surface appearing red and glazed, with numerous small ulcers. In the severe cases, only small islands of mucosa are left, the entire surface being ulcerated, and presenting a granular appearance. The roentgenogram is characterized by marked narrowing and absence of haustrations in the full extent of the involved colon. The connective tissue found in the inner muscular layer may account for these changes. In 4 of the 5 cases, this picture was very definite. In the fourth it was impossible to make a roentgenogram of the colon, because of the acutely tender condition of the rectum. The stools were usually from five to ten in number, containing a considerable amount of mucus and blood, frequently in clots. The passing of blood in clots not intimately mingled with mucus is rather characteristic. Two of the 4 patients had good appetites. There was no harmful after-effect of the eating. The other 3 patients had to be coaxed to eat. Each had considerable tenesmus and cramp-like pains in the abdomen, which may have accounted for the lack of appetite. If there were no complications, the patients were usually free from fever. One patient was a febrile during the entire stay in the hospital. The diagnosis is based on the mucus, associated with the passage of considerable amount of blood, usually in clots. There is a persistence of the dysentery in spite of all medical treatment, and an absence of any of the usual etiological factors. The prognosis is bad under medical treatment. Surgical measures such as colostomy, ileostomy, appendectomy are helpful, with the after-treatment of continuous irrigation through the surgical opening.

Relative Immunity of Infants under Five Months of Age to Infection with Measles.—HERRMAN (*New York State Jour. Med.*, 1923, 23, 404) says that infants under two months of age, whose mothers have had measles are immune. The immunity becomes less marked as they grow older, but even at four or five months of age only 25 per cent are infected. From that time the relative immunity quickly diminishes, so that infants over nine months of age are as susceptible as older children. Artificially fed as well as breast-fed babies enjoy this immunity, with a slight difference in favor the breast-fed infants. This relative immunity during the first months of life also manifests itself in other ways. When young infants are infected with measles, the incubation period may be longer, the fever and constitutional symptoms may be less marked, and the eruption, the catarrhal symptoms and buccal manifestations may be less distinct. The immune substances are probably chiefly conveyed to the fetus through the placental circulation. There is no substantial evidence that any important part of the immunity is due to the ingestion of breast milk.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Marital Syphilis.—STRANDBERG (*Acta Dermat.*, 1922, 3, 546), from a study of 250 marital partners with syphilis, finds the outlook in the marriage of patients with syphilis distinctly discouraging. In only 27.6 per cent did the marital partner escape some consequences of the disease. The transmission of the disease to a healthy partner can take place more than five years after infection in about 20 per cent of the cases and in 2 cases transmission took place after eight years. Syphilitic children can be born as long as ten to fifteen years after the infection of the mother. Manifestations of syphilis may be present in the child at birth even though the mother's infection be three or four years old. In more than 10 per cent of cases a negative blood-Wassermann reaction was obtained from the mothers of syphilitic children. Even the best of treatment during pregnancy may fail to protect the unborn child from infection *in utero*, though the general value of antenatal treatment is conceded. A case is mentioned in which a woman with an active syphilitic infection at her first pregnancy, and practically no treatment, gave birth to a child which has been healthy for many years; but at her second pregnancy, when she was treated with considerable thoroughness, she gave birth to a still-born syphilitic infant. Prolonged observation of children born under suspicion of syphilis is urged.

Acute Disseminate Erythematous Lupus.—VAN DER VALK (*Acta Dermat.*, 1922, 3, 63) comments on a series of cases of acute disseminate erythematous lupus, the grave and usually ultimately fatal constitutional form of the disease, originating in a previous chronic erythematous lupus or appearing without warning. The polymorphism of the eruptive manifestations, with eczematous, erythematous, vesicular, erosive, bullous, pustular, lichenoid and purpuric lesions in contrast to the uniform picture of the chronic type, is emphasized. The frequency of the mistaken diagnosis of erysipelas and the association with pneumonia and uremia should be especially recalled. The writer reviews the etiological conception in this dermatological riddle, referring especially to the contributions of Jadassohn and Barber to the streptococcal factor in the etiology and of Bloch and Fuchs to the tuberculous factor. He mentions the theories of Kreibich and Genenrich, who believe the disease to be the result of toxins elaborated by the lymph nodes under some pathological stimulus. EHRLMANN and FALKENSTEIN (*Arch. f. Dermat. u. Syph.*, 1922, 141, 408), in an elaborate study of a series of 130 cases with autopsy, state, with striking definiteness, their conclusion that erythematous lupus, as they have seen it, occurs in tuberculous individuals in 98 per cent of cases, and is due to tubercle bacilli carried to the skin presumably from the lymph

glands. They consider that acute disseminate erythematous lupus is a tubercle septicemia and that a recent focus of tuberculosis can be found in all these cases.

Arsphenamine in Treatment of Syphilis.—MILLS (*Brit. Jour. Dermat.*, 1923, 35, 131), in discussing the arsphenamine treatment of syphilis, states that in the use of sulpharsenol (sulpharsphenamine) he has experienced very little difficulty with local reaction and finds the drug when given intramuscularly much more rapidly spirillicidal than when given intravenously. In discussing the merits of "606" as compared with "914" (neo-arsphenamine) he unhesitatingly gives the preference to "606" as the more effective therapeutically, even inequivalent dosage, probably, he thinks, because of its slower elimination. He comments on the instability and lack of uniformity of neo-arsphenamine and the inadequacy of therapeutic testing as compared with that enforced in Great Britain in the case of arsphenamine.

Treatment of Dermatitis Venenata.—STRICKLER (*Jour. Am. Med. Assn.*, 1923, 80, 1588) reports upon the use of antigen or toxin for the treatment of dermatitis venenata by desensitization. The preparation of this toxin from plants of the *Rhus* family was previously described (*Jour. Am. Med. Assn.*, 1921, 77, 910). Three to 5 intramuscular injections of this specific antigen were given, the dose ranging from 0.3 to 0.5 cc, although doses up to 0.7 may be given. The first 2 doses are given at two-hour intervals, the remainder at intervals of forty-eight to seventy-two hours, depending upon the response. Marked improvement within twenty-four hours usually occurs, and the skin returns to normal within four or five days. Nearly 95 per cent of 356 patients were markedly improved by this treatment, and the results were vastly superior to the local applications usually used. The process is essentially a desensitization and it is hoped that a larger series in highly susceptible cases will indicate its value as a cure for hypersusceptibility as well as a treatment measure.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Treatment of Patients Pregnant and Tuberculous.—Before a recent meeting of the Association of Obstetricians and Gynecologists, using the French language, THELIN (*Gynec. et obstét.*, 1923, 3, 283) contributed a paper upon this subject. His studies were made in the Maternity Hospital at Lausanne, and the great majority of the patients were in early gestation. In 90 cases the question as to the interruption of pregnancy was considered; in 41 pregnancy was interrupted

and nothing more was done. In other patients 8 sterilizations were performed by excising or ligating the tubes, 1 case aborted and 1 case was afterward studied during and after labor. The indication which seemed to justify the interruption of pregnancy was the fact that the patient's condition became greatly aggravated after pregnancy occurred. The 41 cases in which pregnancy was interrupted are divided into the first group, 9 in number, where the cervix was dilated by a laminaria tent, the ovum was removed by the finger and in a few cases a curette was used in addition. The results were immediately good, 2 patients could not be traced; 4 died of tuberculosis within a year, 3 of the women survived. One of these had again become pregnant and given birth to a healthy child, a second had tuberculosis of the larynx and it was thought best to again interrupt the pregnancy. In the third patient the interruption was practised in 1912, and the patient's condition was complicated by cardiac weakness. Since 1912, 4 pregnancies had occurred, 2 terminated by spontaneous abortion and 2 by the artificial interruption of pregnancy. In the second group, with 6 cases, where pregnancy was interrupted and then the abdomen opened and the Fallopian tubes resected, all recovered from the operation; 1 died three months afterward from tuberculosis and 5 still survive. In the third group, 27 cases, pregnancy was interrupted by incising and emptying the uterus and sterilization was performed by removing the Fallopian tubes. Of the 27, 19 were in comfortable health and able to care for a family or to do active work, 3 could not be traced; 5 had died, 3 of tuberculosis and 2 of influenza. In all, 36 patients had been treated by removing the Fallopian tubes, and in these menstruation had remained regular, the uterus continued to be normal in size and the general health of the patients had been remarkably good.

Vasomotor Tone during Pregnancy.—LOÜROS (*Zentralbl. f. Gynäk.*, 1923, 43, 1667) contributes a paper upon this subject, in which he calls attention to the state of the vasomotor nerves as a symptom of pregnancy. His experiments were made by injecting adrenalin after taking the pulse and blood-pressure with the Riva-Rocci apparatus. Observations were made at intervals of three minutes. In the case of an individual in a normal condition there occurred a gradual rise of blood-pressure which reached its maximum in about fifteen minutes. This was followed by a gradual descent, lasting about fifteen minutes. When, however, there was an increased sensibility in the sympathetic or parasympathetic system, and adrenalin was given, there was a very marked rise in pressure, followed by a great and immediate drop. When there was primary irritability of the parasympathetic system, and adrenalin was injected, the blood-pressure rose very little or, instead of rising, showed signs of sinking. This phenomenon occupied about ten minutes. After this method, experiments were made upon pregnant women at each month of gestation and also of women in labor and who had been delivered. Thirty-eight patients were examined and in none of these was the condition of vasomotor tension found to be normal. In 32 there was the condition called parasympathetic or vagotone, and in 6 there was little or no reaction, indicating an abnormal condition of the sympathetic system. The 32 patients

did not describe symptoms which especially drew attention to the condition. One complained of excessive perspiration; variations of the pulse-rate were present; in some abnormalities in the pigmentation of the skin were also observed. These abnormalities disappeared at the termination of pregnancy. In the 6 women who had the condition known as sympathetic sensibility, there was a very considerable rise in pressure after the injection of adrenalin. This was followed by rapid descent. Most of these patients showed irregular action of the heart, difficulty in respiration, heart murmurs and other symptoms of undue sensibility. In 1 of these patients, after the pregnancy terminated, the same symptoms persisted for some time. The writer also adds to his paper the adrenalin blood-pressure curve of 22 eclamptics. In 17 of these, five minutes after adrenalin was injected, the blood-pressure, which previously had been high, sank rapidly, free perspiration was also present and in 14 there was positive evidence of implication of the endothelia of the vessels. In 6 patients there were symptoms of hyperthyroidism. The writer concludes from these observations that during pregnancy there is a condition of the vasomotor nerves which indicates a parasympathetic state. This serves to mask and compensate for many disturbances during pregnancy. In toxic patients with eclampsia this condition is very greatly exaggerated. While we do not know the exact cause of this, it undoubtedly has to do with the condition known as toxemia of gestation.

Hydatidiform Mole and Chorio-epithelioma.—GORDON (*Surg., Gynec. and Obst.*, 1923, 36, 242) at the Bellevue Hospital, finds that in 4500 abortions there were discovered 21 hydatidiform moles, a percentage of 0.4, other cases may have been overlooked. The mortality of this series was 9 per cent and this was from a low grade of sepsis following moderate but prolonged bleeding. In the Laboratory of the Bellevue Hospital in 8000 autopsies and with the examination of more than 3500 surgical specimens, there has been identified but one chorio-epithelioma, and this was a metastatic growth of the vulva and was considered as doubtful. Probably chorio-epithelioma does not occur more frequently than a fraction of 1 per cent. Statistics vary as to the frequency in which chorio-epithelioma follows hydatidiform mole. In the writer's experience it is rare. So far as treatment is concerned, the writer urges the substitution of abdominal hysterotomy for curetting and other methods formerly advised. If the condition of the cervix permits, the uterus may be thoroughly explored by the fingers, and the abnormal tissues may safely be removed with little danger. The uterus can then be palpated and its interior carefully studied and if there be found a soft and friable area in the myometrium, hysterectomy is advisable. If the uterus be manually emptied and allowed to remain, these patients should be kept under observation and hysterectomy be performed should hemorrhage return. Unless the fingers can readily gain access to the uterus and examine its cavity, abdominal section with incision into the uterus and thorough examination is indicated. By this method pathological tissues in the uterus can be safely removed and the uterus saved. If on performing section there is undoubted evidence of chorio-epithelioma, hysterectomy is indicated. Not only changes in the uterus but in some cases extensive thrombosis of the pelvic veins are signs of

this malignant condition. Theoretically the use of radium or deep roentgen-ray treatment should be of advantage but there is no record of the trial and results of this method. In from 80 to 90 per cent of cases bilateral ovarian cystomata are present. As a rule these growths are short lived and probably arise from distention and overgrowth of corpora lutea, they usually disappear spontaneously after the abnormal condition of the uterus is remedied. Hydatidiform degeneration of the chorion, the writer believes is infrequent, and actual chorio-epithelioma from his observation is extremely rare. The relative malignancy of a given growth can be accurately distinguished by microscopical examination only. The methods already described by the writer are urged and curetting is considered dangerous and practically worthless as a means of diagnosis.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Intracervical Enucleation.—LAHEY (*Ann. Surg.*, 1923, 78, 61) directs attention to this method of intracervical enucleation for removal of the cervix in hysterectomy for benign lesions, because in his hands it has proven such a rapid, safe and satisfactory measure for the accomplishment of this purpose. It consists in the routine supracervical hysterectomy as done, for example, for fibroid uterus up to the point of section of the cervix. At this point the cervix is not cut across or even removed by wedge-shaped excision, but is cored out by vertical-circular incisions placed just within the outermost boundary of the cervix. The cervix is pulled up with each circular incision, until as the last incision reaches the vagina the thin remaining shell of cervical tissue is inverted from below upward, to drop back as the last circular incision separates the cervical plug from its shell of remaining cervical tissue. This leaves an opening through which a small strip may be tucked into the vagina to prevent the possible return of infected vaginal contents. The stumps of the round, and if need be the broad, ligaments fit easily into the large aperture and may be sutured securely there. It is usually necessary to place a large mattress stitch through the entire cervical shell to control the oozing which occurs from the walls from the remaining shell. Lahey has used this method of getting rid of the cervix in hysterectomy for benign lesions to overcome the postoperative leucorrhea without producing the vaginal shortening which results from the employment of complete hysterectomy. The disadvantages of the procedure have

been, first, the excessive oozing from the cervix during the process of coring, resulting often in a pooling of blood at the bottom of the pelvis and producing a somewhat messy condition at this stage of the procedure. This may be overcome in some measure by folding a towel into a triangular shape and introducing the apex into the fossa of Douglas, so that any ooze is caught in the hollow of the towel so placed. This oozing has been immediately controlled as soon as the cervical mattress suture has been tied. The operation is but little prolonged, there is no danger to the ureters and excellent support can be obtained by the fixation of the round and broad ligaments as deeply as desired in the remaining cervical aperture.

Value of Cervical Surgery.—No part of the female genitalia has received so much attention in recent years as the cervix uteri. Endless papers and monographs have been written upon the remote effects of the lacerated and infected cervix. For this reason it seemed to POLAK (*Am. Jour. Obst. and Gynec.*, 1923, 5, 640) that it might be well to determine what constitutes the surgical cervix and how much pathology must exist before we are justified in subjecting the patient to excision, trachelorrhaphy, tracheloplasty or amputation. Therefore, he has reviewed the records of 350 operations upon the cervix, analyzed the indications for the procedures and the end-results as to the effect on sterility, discharge, pregnancy and labor. Critical study of this series shows that operation on the surgical cervix, *i. e.*, for extensive or multiple lacerations, extensive erosion with hyperplasia or cystic degeneration, even when the type of operation is carefully selected, in a large number of cases does not cure the leucorrhea or sterility, and that unless the operation is preceded by a long period of preliminary local treatment the leucorrhea is cured in only a little more than 50 per cent of the cases operated upon. It is therefore urged that all operations on chronically infected cervixes be preceded by local treatment. Only a relatively small number of sterilities are cured by operations on the cervix, and these should only be done for this cause after a Hühner and a Rubin test have shown that the fault is in the biochemical changes in the cervical discharge. After amputation or excision should pregnancy occur it is more likely to terminate in abortion than has been the case when trachelorrhaphy has been selected. Dystocia during labor is also more common after amputation and excision than after cervical repair.

Hysteropexy for Prolapse of the Uterus.—In recommending the performance of hysteropexy in the treatment of uterine prolapse, MAXWELL (*China Med. Jour.*, 1923, 37, 393) is aware that this operation is supposed to be unsafe, owing to the possibility of intestinal obstruction following on the stretching of adhesions, a band being left between the uterus and the point of fixation. Of 45 patients on whom he had performed this operation all were alive except 2, who died from diseases having no relation to the uterine trouble. In answer to the statement that hysteropexy interferes with the expansion of the uterus in the event of a subsequent pregnancy, the author states that there have been 20 pregnancies subsequent to operation in his series, all of which were normal. He believes that the bad name which hysteropexy has

acquired is due in large part to the poor technic which has been employed. A number of operators have placed their sutures in the fundus of the uterus, some even anteverting the organ by a suture passed through the top of the posterior wall. Some operators leave non-absorbable sutures permanently uniting the uterus to the abdominal wall. In the former procedure (anteverting the uterus), if the attachment to the abdominal wall holds it is quite evident that by no possibility can the uterus enlarge normally, but must do so at the expense of the posterior wall alone, with the risk of rupture of the uterus or malpresentation. In the second procedure any buried permanent sutures are likely to affect the regular expansion of the uterus and entail the same risks as in the former case. While no operation for prolapse has proven perfectly effective in all cases, the author believes that hysteropexy will permanently cure the bulk of patients and relieve a considerable proportion of the rest. Of 39 cases which he has been able to follow closely there have been recurrences in 5, which means a successful result in 87 per cent. Of the recurrences 2 recurred after childbirth, 1 recurred due to increased intra-abdominal pressure due to a rapid splenic enlargement, while the other 2 cases recurred for no reason that could be discovered.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Complement-fixation Reaction as Applied to Leprosy.—Many have endeavored to use the reaction of complement-fixation as a means of increasing our knowledge of leprosy, either in making a certain diagnosis or to determine an etiological relationship to the disease. In no instance have these efforts to apply complement-fixation been eminently successful. By utilizing many facts and ideas evolved from an extensive experience with complement-fixation in tuberculosis, LEWIS and ARONSON (*Jour. Exper. Med.*, 1923, 38, 219) developed a new method for testing 45 specimens of sera obtained from 39 cases of leprosy. The antigens employed were many and consisted of bacillary emulsions of *B. lepræ* (Clegg), *B. lepræ* (Duval), *B. lepræ* (Kedrosky), *B. smegmatis*, timothy hay bacillus, Must bacillus, etc.; as well as alcoholic extract of bovine *B. tuberculosis* and *B. lepræ* (Clegg), Petroff's antigen and cholesterol and acetone antigens of human heart. The test was performed by adding to 0.1 cc of the serum antigen, 2 units of complement and sufficient salt solution to bring the total volume to 1 cc. After incubation for two hours at 37° C. 4 units of anti-sheep amboceptor

and 0.1 cc of a 5 per cent suspension of sheep cells were added. After thirty minutes incubation in the water bath and again, after overnight in the ice-box, the results were noted. After various experiments, it was found that the blood serum of cases of leprosy exhibited the ability to fix complement with a wide variety of antigens including to a greater or less extent those derived from any of the acid-fast group of bacteria available to the authors. Control sera from normal individuals, from cases of tuberculosis, or from cases of syphilis entirely failed to react with certain antigens, whereas serum from cases of leprosy so reacted to the extent of over 93 per cent. The most characteristic fixation given by the leprosy sera was that with *B. lepræ* (Clegg) used as antigen, either in the form of a bacterial emulsion or of an alcoholic extract of the dried culture. Antibody absorption could be demonstrated in the acid-fast group if the absorbing bacteria were removed by filtration. Otherwise the resulting fluid was strongly anti-complementary. Leper serum was not deprived of the complement-fixing body when so treated with either *B. tuberculosis* or *B. lepræ* (Clegg.)

A Study of Rabbit Spirochetosis.—Since 1912, several investigators have noted the occurrence in rabbits of a spontaneous venereal spirochetosis resembling syphilis, in the lesions of which a spirochete, very similar in appearance to *Treponema pallidum* and named *Treponema cuniculi* by Noguchi, has been demonstrated. As a result the value of all the experimental work on rabbit syphilis is challenged. Realizing the importance for more extensive studies at this time, WARTHIN, BUFFINGTON and WANSTROM (*Jour. Infect. Dis.*, 1923, 32, 315) reported their findings in a detailed investigation of the cuniculi disease, basing the study on the disease as produced experimentally in 18 rabbits which were inoculated by scarification from a spontaneous case found in a Western rabbit. The lesion, so produced, was a superficial one, papillomatous or condylomatous in character, limited to mucous membranes or skin, which spread by contiguity, continuity or autoinoculation and could be transmitted by inoculation, contact and coitus. The lesions were essentially epithelial and not vascular, being confined to the epithelial surface and upper portion of the subepithelial tissues, with marked hyperplasia of the epithelium and papillary layer. Histologically, the spirochetosis did not suggest chancre. No evidence of systemic infection was found and no lesions containing spirochetes occurred in any of the internal organs. The incubation period varied from 5 to 56 days, averaging 23.81 days for 16 inoculations. The general health of the infected animals remained good save in the event of intercurrent infections. The Wassermann reaction was negative and no general immunity was developed. From the lesions the spirochetes could readily be obtained by cover-glass smears of the surface or by scarification and could be best demonstrated by the WARTHIN-STARRY silver-agar method for cover-glass smears (*vide Jour. Infect. Dis.*, 1922, 30, 592). The organisms resembled some of the mouth spirochetes more closely than *Treponema pallida*, than which they were usually thicker and larger, as well as softer and more flexible, tending to form circles, V and Y shapes and twisted stellate forms. In sections of tissue lesions, the cuniculi lay in entangled masses on and in the epithelium, and just below it, rarely penetrating in any appreciable numbers deeply into

the tissues. The authors indicate that cuniculi spirochetosis does not resemble syphilis in its clinical course or in its local or general pathological picture and should not be called "rabbit syphilis." Moreover, they say that the spontaneous rabbit disease can be easily differentiated from pallida infections by its morphology, as shown in a silver-agar cover-glass smears and by the pathology of the lesions. They believe, however, that it will be necessary to repeat much of the experimental work in this new light, inasmuch as "too many important deductions have been made from rabbit experimental work to admit of any doubt being allowed to remain as to their accuracy."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Studies on Pneumococcus Immunity. II. Active Immunization of Monkeys with the Homologous Pneumococcus Vaccine.—CECIL and STEFFEN (*Jour. Exp. Med.*, 1923, 38, 149) state that three subcutaneous injections of Pneumococcus Type II vaccine confer on monkeys a complete immunity against experimental Pneumococcus Type II pneumonia. A similar protection can be bestowed on monkeys against Pneumococcus Type IV pneumonia by three subcutaneous injections of a vaccine prepared from the same strain of pneumococcus. The subcutaneous injection of monkeys with three doses of Pneumococcus Type III vaccine confers a complete immunity against this type in only 50 per cent of cases (4 out of 8 monkeys vaccinated). In spite of the immunity induced in monkeys by three subcutaneous injections of Pneumococcus Types II, III and IV vaccine, specific protective bodies against the homologous types are not demonstrable in their serums when the vaccine is so administered.

Schick Tests and Immunization Against Diphtheria in the Eighth Sanitary District of Vermont.—KIDDER (*Public Health Reports*, 1923, 38, 663) gives the following conclusions: (1) That both the percentage of susceptibles and the degree of susceptibility to diphtheria are higher in sparsely populated sections than in thickly settled or urban communities. (2) That the percentage of susceptibles among rural people, without regard to class or environment, is higher than that of the well-to-do classes in cities. (3) That in the rural districts, as well as in the cities, the percentage of susceptibles is much higher among the well-to-do than among the poorer classes. (4) That the percentage of suscep-

tibles is much higher among the native born than among the foreign born. (5) That age is a relatively unimportant factor in the immunization of individuals living in strictly rural communities. This conclusion is supported by the fact that of 87 teachers between the ages of twenty and sixty years, included in the group of 2030 persons tested, 82 per cent gave positive Schick reactions. It was found also that the degree of susceptibility as evidenced by Schick reactions was as high among the susceptible adults as among the susceptible school children. (6) That the higher the degree of susceptibility the less reaction there is to toxin-antitoxin. (7) That those individuals having a positive combined Schick reaction are more likely to have a severe reaction from toxin-antitoxin. (8) That notwithstanding the distances to be covered and the other factors in the relatively high cost and difficulties of such work in rural districts, the use of the Schick test and of toxin-antitoxin for immunization against diphtheria is, in view of the extent and degree of susceptibility to the disease and the frequent lack of facilities for prompt and adequate treatment of cases, especially important in rural communities and should be included at appropriate times in the program of activities of rural health departments.

Changes in a Small Town Brought About by the Health Department.—BAGBY (*Public Health Reports*, 1923, 38, 456) contrasts medical practice of 1909 with that of 1922, and draws attention to the difference, due to public health measures. Malaria, typhoid fever, hookworm infestations and intestinal diseases have largely disappeared. Improved milk supply, satisfactory water and sewage systems, drainage against malaria and improved housing conditions account for the improvement.

A Bacteriological Study of Vulvo-vaginitis of Children.—ANDERSON, SCHULTZ and STEIN (*Jour. Infect. Dis.*, 1923, 32, 444) found that in a series of 42 cases of vulvo-vaginitis among children reporting to a dispensary clinic for treatment, 37.5 per cent were due to the gonococcus and 64.3 per cent were non-specific. In 53.3 per cent of the specific cases, the gonococcus was isolated in pure culture. In the remainder, the specific diagnosis was based on the presence within leukocytes of morphologically typical, Gram-negative diplococci. Although the newer cultural methods have simplified the isolation of the gonococcus, the direct smear examination should be given preference over the cultural method as a diagnostic procedure. In no case was it possible to cultivate the gonococcus when gonococcus-like bacteria were not detected in the smear examination. It was impossible, by immunological methods, to differentiate the gonococci isolated from children from those derived from women. In the non-gonorrheal cases a mixed flora was present, but streptococci of intestinal origin appeared to be the most important agents. Staphylococci, colon bacilli and Gram-positive bacilli were frequently encountered, probably as secondary invaders or harmless symbionts. Uncleanliness and local irritation are believed to be an important, and probably the primary, factor in the non-specific cases, the condition thus established being maintained or made worse by bacterial localization. In the latter part of the process, bacteria of intestinal origin appear to be most important. Cases in which

filth and irritation appeared to be the chief factors yielded most readily to the routine therapeutic procedures which were applied in all cases. The gonorrheal cases were most stubborn. In an intermediate position, as regards the readiness with which they yielded to treatment, were the cases in which local irritation was followed by the localization of bacteria other than the gonococcus. Quarantine and exclusion from school are not believed to be necessary in the non-gonorrheal cases.

Further Notes upon Experimental Measles in Rabbits and Monkeys.—NEVIN and BITTMAN (*Jour. Infect. Dis.*, 1923, 32, 33) passed the virus of measles obtained from patients on the second day of the disease through 4 rabbits and then produced symptoms typical of measles in a monkey. In a second series the virus was passed through 3 rabbits and then through 3 monkeys in which symptoms typical of measles were produced. The monkey-to-monkey passage eliminated any question of rash due to foreign protein. A control monkey injected with normal human blood showed no reaction. The authors state that the results of these two series of passages confirm their previous findings that the virus of measles survives rabbit passage and produces symptoms typical of measles in the monkey (*M. rhesus*).

The Devil's Grip in Virginia.—ARMSTRONG (*Pub. Health Rep.*, 1923, 38, 1964) reports an epidemic in which the outstanding features are: Patients usually children, often several in a home; onset sudden, with acute pain, generally of the epigastrium, later shifting to one side of the chest; shallow, painful, rapid respiration; temperature, 101° to 103° F.; often symptoms variable, and all transitory, usually subsiding in twelve to thirty-six hours. Physical examination negative. This was considered to be identical with the disease described by Dabney in 1888.

Does Commercial Pasteurization Destroy Tubercle Bacilli in Milk.—BARTLETT (*Am. Jour. Public Health*, 1923, 8, 807) conducted experiments to determine whether commercial pasteurization renders milk safe from the standpoint of tuberculosis and found that pasteurization by the holding method between 142° F. and 148° F. for thirty minutes destroys the tubercle bacillus in milk. Specimens of raw milk taken from mixing vats holding from 300 to 1200 quarts each showed the presence of tubercle bacilli by guinea-pig inoculation in 50 per cent (44 per cent). The relative frequency with which tubercle bacilli were found was greater in milk from the larger mixing vats than in that from the smaller mixing vats.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL*.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript*.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MARCH, 1924

ORIGINAL ARTICLES.

THE CLINICAL SIGNIFICANCE OF THE PATHOLOGICAL
CHANGES IN HODGKIN'S DISEASE.

BY DOUGLAS SYMMERS, M.D.,

DIRECTOR OF LABORATORIES, BELLEVUE AND ALLIED HOSPITALS, NEW YORK.

(From the Pathological Laboratories of Bellevue Hospital.)

(Continued from February, 1924)

Group II. Involvement of the Lymphoid System and Destruction of Tissues Beyond It. CASE XI. *Destruction of Muscle Tissues.*—P. B., aged forty years, was admitted to Bellevue Hospital, August 1, 1921, and died January 10, 1922. The patient stated that three years previous to admission he had noticed enlarged nodes in the left axillary region. Eight months before admission he began to suffer from pain in the back, radiating to the hips and knees. Two months before admission he noticed gradual swelling of the tissues in the region of the left anterior chest wall and left axilla, attended by painless swelling of the corresponding arm and later by swelling of the legs and scrotum. Before coming to Bellevue Hospital he had been a patient in the Brooklyn Hospital, where, he stated, that a large quantity of fluid had been removed from the left chest. Dr. James Denton, at that time pathologist to the Brooklyn Hospital, removed a portion of tissue from the region of the left pectoralis major muscle. Upon microscopical examination this tissue presented the histological characteristics of Hodgkin's disease.

At the time of admission to Bellevue Hospital physical examination revealed slight enlargement of the cervical lymph nodes on

both sides and in the left supraclavicular fossa and left axilla. There was immense swelling of the left anterior chest wall, and the respiratory excursions on this side were limited. The percussion note over this area was flat, the voice sounds harsh, with fremitus absent. The left upper arm and the left thigh and both feet and ankles were edematous. The spleen was not palpable. The blood revealed hemoglobin, 65 per cent; red blood cells, 4,200,000; leukocytes, 17,500, of which there were 80 per cent polymorphonuclear neutrophiles, 9 per cent lymphocytes, 3 per cent mononuclear cells and 2 per cent transitional cells. On December 18 a quantity of thick pus was evacuated from the left chest, and on January 5 thoracotomy was done and a collection of pus was removed from the left lower part of the pleural cavity and the cavity drained.

Duration of symptoms: Three years and five months.

Autopsy Findings. Hodgkin's disease with enormous enlargement of the abdominal and thoracic lymph nodes and thickening of the left pleura, penetration of the chest wall and infiltration of the intercostal and pectoral muscles on the left side; extensive replacement of the vertebræ; nodules in the spleen and pericardium.

Histology. Microscopical examination of the lymph nodes and spleen showed a fibroblastic stroma in which were innumerable lymphocytes, numbers of mononuclear giant cells, a profusion of multinuclear giant cells and a fair abundance of eosinophiles. Sections from the intercostal muscles on the left side showed numbers of cells of identical histology with those encountered in the lymph nodes. They were strewn between the muscle bundles in such manner as to push them apart or to destroy and replace them. The corresponding pleura was immensely thickened and sclerotic. The free surface was covered by a thin layer of degenerate polymorphonuclear neutrophiles between which and the lung were streak-like or insular collections of lymphocytes, multinuclear and mononuclear giant cells and a few eosinophiles.

Comment. The enormous enlargement of the abdominal lymph nodes, together with the history of pain in the back radiating to the hips and knees, and the relatively slight involvement of the superficial nodes indicate that the primary manifestations of the disease were in the nodes of the abdomen, although simultaneous thoracic changes are not to be denied. The most striking feature of the case, of course, is to be found in involvement of the pleura, penetration of the chest wall and destruction of the muscle tissues covering the side of the chest. The association of Hodgkin's disease of the pleura with empyema constitutes a feature which, in my experience at least, is unique.

CASE XII.—J. R., aged fifty-five years, was admitted to Bellevue Hospital, August 8, 1921, and died on December 31 of the same

year. The patient stated that three months before admission he noticed a dull aching sensation in the region of the angle of the right scapula. A few days later the right index finger was paralyzed and devoid of sensation. Two days after this the ring and little finger on the same side became similarly involved. In the course of the four months previous to admission the patient stated that he had lost 19 pounds in weight and that about three weeks before admission he had observed a painless lump in the right side of the neck and a slight cough.

At the time of admission physical examination revealed numerous discrete and movable nodes at the root of the neck, more especially on the right side. In the corresponding axilla there was an enlarged node and an area about 15 cm. in diameter, in which there was loss of the sensation of touch, pain and temperature, together with hypersensitiveness along the vertebral column corresponding to the margin of the scapula. The right arm was weaker than the left and atrophied. Examination of the chest showed some limitation of expansion on the right side. The heart sounds were muffled. During the four months that the patient was under observation at Bellevue Hospital enlarged nodes appeared in the left axilla and in the left groin. Blood count was 4,400,000 red cells; hemoglobin, 85 per cent; polymorphonuclear neutrophils, 78 per cent; lymphocytes, 17 per cent; mast cells, 5 per cent.

Duration of symptoms: Approximately eight months.

Autopsy Findings. Hodgkin's disease of the cervical, axillary, inguinal, anterior mediastinal, periaortic and peripancreatic lymph nodes, with infiltration and replacement of the pectoral and psoas magnus muscles on the right side and the outer half of the pancreas; nodules in spleen; hydrothorax.

Histology. Microscopical examination of enlarged lymph nodes removed from different parts of the body showed rearrangement of the normal architecture due to the overgrowth of cells of the lymphocytic type, scattered among which were numbers of large mononuclear cells and a sprinkling of multinuclear giant cells, together with an occasional cell of the eosinophilic variety. In some of the nodes discrete areas or intercommunicating streaks of anemic necrosis were present, and in places an attempt was evident to replace these by newly formed connective tissue, with or without the presence of thin-walled bloodvessels. In lymph nodes removed from the abdomen, in addition to the changes just outlined, it was to be seen that the neighboring fat tissues were infiltrated by cells of the same sort, and that the walls of the medium-sized bloodvessels were invaded, providing a cellular mantle of voluminous proportions with compression of the lumen. The lumina of the small vessels were likewise frequently reduced because of the dense cellular infiltrate in which they were imbedded, aided in many instances, however, by heaping up of their lining endothe-

lium. Thromboses were sometimes to be seen both in the medium-sized and small vessels, the vascular lesions thus accounting for the necrotic areas. Much the same changes were to be found in the invaded muscle tissues—the muscle fibers were separated and partially or totally replaced by cells of the same type as those occurring in the lymph nodes and elsewhere. The walls of blood-vessels were infiltrated and nerve fibers were surrounded but rarely penetrated. In the spleen the nodular foci were composed of a preponderance of lymphocytes, among which were variable numbers of large mononuclear cells and an occasional multinuclear giant cell. Necroses were numerous, and at intervals the necrotic areas were partially replaced by granulation tissue. The adventitia of the abdominal aorta was infiltrated and banked by a collection of the same sort of cells, but the media and intima were free. Sections from the deep axilla showed large nerve trunks imbedded in and frequently penetrated by the same cellular composite.

Comment. This patient presented the picture of involvement of the lymph nodes of the neck, thorax, abdomen, axillæ and groins, with destruction of the muscles of the chest on the right side and of the right psoas magnus, together with invasion of the fat tissues of the abdomen and of the walls of the small bloodvessels and of the outer walls of the aorta, replacement of the outer half of the pancreas and nodular involvement of the spleen. In spite of this widespread destruction of tissues, the patient presented no clinical signs or symptoms indicative of disturbances in the chest or abdomen other than a slight cough which, incidentally, he attributed to cigarettes. It is interesting to observe that, clinically, the case was marked by progressive but not extensive loss in weight and by the symptoms of pressure neuritis of the right arm.

CASE XIII.—The patient, T. B., aged forty-seven years, was admitted to Bellevue Hospital, November 7, 1913, and died on January 15, 1914. The patient stated that nine months previous to admission she noticed a growth the size of a pea at the side of the nose. A month later the growth was removed in another hospital, together with the nodes of the neck.

On admission to Bellevue Hospital physical examination showed enlarged nodes in front of the right ear and in both submaxillary regions, together with numerous smaller ones in the left posterior cervical triangle, a large mass in the right axilla and nodules on the inner side of both arms and forearms, in both inguinal regions and in the left thigh. The tonsils were enlarged. Red blood cells numbered 4,912,000; white cells, 6600; polymorphonuclear neutrophils, 66 per cent; lymphocytes, 20 per cent; large mononuclears, 10 per cent; transitionals, 4 per cent.

Duration of symptoms: Eleven months.

Autopsy Findings. Hodgkin's disease, with predominant enlargement of the peribronchial and abdominal lymph nodes; moderate enlargement of the lymph nodes of the neck and groin; multiple nodules in lungs, liver and bone-marrow of right femur; hyperplasia of both tonsils; multiple nodules beneath the skin of the trunk, arms and the lower half of the left leg; infiltration of the muscles and tendon sheaths of the right forearm directly continuous with the nodules beneath the skin of the part.

Histology. The lymph nodes revealed a fibroblastic reticulum lodged in which were innumerable cells of the lymphocytic and plasma type, eosinophiles and eosinophilic myelocytes, large mononuclear cells and a liberal sprinkling of multinuclear giant cells. Sections prepared from the bone-marrow of the ribs which, grossly, was abundant and reddish, but otherwise unchanged as far as the unaided eye could determine, revealed, on microscopical examination, changes not to be distinguished from those in the lymph nodes, including conspicuous numbers of multinuclear giant cells. The latter were of two sorts: One was a large cell with lobulated or overlapping nuclei and smooth, faintly acidophilic cytoplasm, corresponding morphologically to the myeloplques of the normal bone-marrow; the other was a cell of slightly smaller size, with smooth, slightly basophilic cytoplasm and a hyperchromatic nucleus of variable shape—angulated or jagged, square, roughly rectangular, ovoid or otherwise atypical. This variety of giant cell, as far as I am aware, is without a prototype in the normal marrow; I have seen it in the marrow in conditions other than Hodgkin's disease, notably in syphilitic anemias of the pernicious type, but never in normal circumstances. In the case under discussion it occurred in the marrow of the ribs with noticeable frequency, and on comparing it with the giant cells encountered in microscopical preparations of the lymph nodes, lungs and tonsils from the same body it became apparent that the latter structures contained an identical variety of giant cell in numbers—a fact which tends to justify the conclusion that it found lodgment in these places as a result of discharge from the marrow by the process of embolism. Microscopical examination of the nodules in the lung revealed an histology practically the same as that of the lymph nodes, as did the nodules in the liver and the enlarged tonsils. In the skin the nodular masses were composed of vast numbers of cells of the lymphocytic type, among which were fairly numerous large mononuclear cells and, rarely, a multinuclear giant cell. Eosinophiles were not detected. The cellular infiltrate pushed its way upward to the epithelial stratum, but never beyond it, so that ulceration did not occur, and in a downward direction it separated collagen fibrils and surrounded and invaded the sweat and sebaceous glands. Microscopical examination of the muscle structures of the forearm showed the presence of a richly cellular

growth, presenting essentially the same histological characteristics as the lymph nodes, lung, etc.

Comment. This case merits remark in that the spleen was normal in size and otherwise intact. At the same time there were nodular formations in the lungs, liver and skin with infiltration and destruction of the muscles and tendon sheaths of the right forearm. The giant cells in the bone-marrow were of two sorts, typical and atypical, and morphologically indistinguishable forms were found in the lymph nodes, lungs and liver. It appears, therefore, that in the latter situations they were most probably derived from the bone-marrow by the process of embolism.

CASE XIV. Predominant Enlargement of the Thymus in Hodgkin's Disease.—J. E., female, aged thirty-two years, was admitted to Bellevue Hospital, May 1, 1917, and died June 17, 1917. She complained of "asthmatic" attacks of two years' duration. In the past year difficulty in breathing had increased to such an extent that she was unable to lie down night or day.

At the time of admission orthopnea was distressing and both upper extremities and the anterior chest wall were edematous. Over the right side of the chest anteriorly the percussion note was flat and expiration was high-pitched and hissing, although not frankly bronchial, and the voice sounds were high-pitched and increased in quality. The spleen was not felt. The edge of the liver was palpable about 5 cm. below the right costal slope, and there were signs of fluid in the left chest. During the seven weeks that the patient remained in the hospital the left chest was tapped five times and on each occasion from 1000 to 1500 cc of fluid were removed. The roentgen-ray report was to the effect that there was a large area of diminished illumination in the right pulmonic field, which was interpreted as due to a tumor in the anterior mediastinum. Red cells numbered 2,400,000; leukocytes, 11,000, of which 80 per cent were polymorphonuclear neutrophiles. Wassermann reaction was negative.

Duration of symptoms: Two years and seven weeks.

Autopsy Findings. The anterior chest wall was edematous. On opening the body a growth was apparent in the region normally occupied by the thymus. The growth measured 25 cm. in length and 18 cm. in thickness and was firm in consistence. It presented a whitish or faintly cream-colored substance and extended downward in such manner as to obliterate the upper part of the right pleural cavity and to invade and replace almost the whole of the two upper lobes of the right lung. The lower lobe of the lung was not involved. Scattered through the substance of both lungs were numbers of large and small, circumscribed nodules made up of tissue of identical appearance with that in the main growth. The peribronchial nodes were greatly enlarged, as were those

lying at the sides of the esophagus. The cervical and abdominal nodes were unchanged. The left pleura enclosed about 2000 cc of clear yellow fluid. The spleen was slightly enlarged, but was not nodular.

Histology. Microscopical examination of the growth in the thymic region showed a connective-tissue reticulum supporting great numbers of lymphoid cells, among which were prominent numbers of large mononuclear cells and an occasional multinuclear giant cell of the myeloid type. These giant cells exhibited a tendency to arrange themselves focally. Microscopical examination of the peribronchial lymph nodes revealed large collections of lymphocytes, among which were mononuclear and multinuclear giant cells, the islands being separated by rather coarse bands of mature connective tissue. In places these islands were permeated and partially or completely replaced by a dense, pinkish staining, poorly nucleated, hyaline reticulum, such as has been described elsewhere in this paper as a local attempt at healing. The nodules in the lung were made up almost exclusively of lymphoid cells, but among them were disclosed a few mononuclear giant cells and, rarely, a multinuclear cell of the myeloid type. Moderate numbers of eosinophiles were to be seen, usually at the periphery of the lymphoid collections. The spleen and liver were microscopically well preserved.

Comment. This is an example of Hodgkin's disease of the thymus body. I know of only 4 similar cases—one described by Yamasaki, a second by Chiari, a third by myself and a fourth by Lyon.

In Yamasaki's case¹¹ a woman, aged thirty-two years, presented a huge mass in the anterior mediastinum that imitated the normal shape of the thymus. It covered the precordium and penetrated the parietal pericardium at several points. The growth invaded the pleura of the right lung and the substance of the lung itself. The sternum was eroded by direct contact and the walls of the left innominate vein and of the superior vena cava were infiltrated. The lymph nodes in the neck and in the region of the stomach were enlarged, the former appearing six weeks before death.

In Chiari's case¹² the subject was a woman, aged twenty-three years. At necropsy a mass was present in the anterior mediastinum and was described as approximating the size of a child's head. The growth was continuous with nodular masses which extended into the neck on both sides as far as the level of the thyroid cartilage, and with knob-like projections in the parietal pericardium on the right side. The trachea and larger bronchi were surrounded by nodular growths. In one of the larger bronchi the lumen was compressed and the walls were invaded; the mucosa appeared elevated, but otherwise intact. The esophagus was laterally displaced. Whitish nodules were imbedded in the pleura on the right

side. The spleen was enlarged and slightly nodular, and the lymph nodes at the head of the pancreas were described as about the size of pigeons' eggs.

In Lyon's case¹³ the patient was a boy, aged twenty years, who, at necropsy, presented a growth in the thymic region that measured 12 by $7\frac{1}{2}$ cm. The right lung was extensively invaded and replaced. Anteriorly the growth eroded its way through the chest wall, producing a large ulcerated area in the skin. In addition there was enlargement of the thoracic and abdominal nodes. The cervical nodes were not involved. The spleen was about normal in size, but not nodular. The patient gave a history of respiratory distress over a period of about one year and four months.

My first case¹⁴ was that of a woman, aged fifty-six years, who during life complained of cough, dyspnea and palpitation of the heart. There was edema of the neck and right chest wall and left-sided hydrothorax. At necropsy a whitish, firm, slightly lobulated growth was found in the upper anterior mediastinum, approximating the shape of the thymus and measuring 18 cm. from above downward and 11 cm. in a transverse direction. The mass projected through the superior aperture of the thorax and invaded the lower pole of the right lobe of the thyroid gland for a distance of 3 cm. In a downward direction it covered the upper part of the precordium and displaced the heart to the left. On the right side it compressed but did not invade the lung. Posteriorly it compressed the trachea and invaded its walls for a distance of 8 cm. The mucous membrane throughout this area presented a series of small projections, but no signs of ulceration. There were numbers of slightly enlarged lymph nodes in the lower part of the neck, but the abdominal nodes and the spleen were not involved.

My second case is outlined above and calls for no further comment other than that it represents an almost exact counterpart of the four just synopsised.

In all of these cases the histological changes described in the mediastinal growths, in their continue extensions and in the more remote nodules are in complete agreement with the histology of Hodgkin's disease as observed in other cases in the lymph nodes and elsewhere.

These 5 cases, described by four independent observers, and recorded from the clinical, anatomical and histological viewpoint, unite, I think, to establish Hodgkin's disease of the thymus body as a clinical and pathological entity.

The Lymph Nodes in Hodgkin's Disease. The term "primary Hodgkin's disease" is often used as a matter of expediency to indicate the greatest degree of enlargement of the lymphoid structures as encountered anatomically and as representing, presumably, the oldest lesions. The term, however well it may fit into everyday usage, is to be avoided in that it is apt to convey a false con-

ception of the pathology of Hodgkin's disease, which has multiple foci of origin occurring at the same or approximately the same time in the lymph nodes of the same or of separate groups, and in that the nodes of one group may enlarge progressively while those of another group may recede or remain stationary; at least for a while. Nevertheless, if one bears these facts in mind it is often practicable to arrive at a reasonably safe conclusion as to the comparative age of the respective enlargements, whether of the lymph nodes proper or of such lymphoid organs as the spleen and thymus, and thus to provide a classification of working value.

The clinical arrangement outlined and followed in this paper is founded partly on these facts and partly on an arbitrary division of the lymph nodes of the body into three great groups, and on the circumstance that, in Hodgkin's disease, the individual groups react differently.

(a) Included in the first group are the lymph nodes of the *neck, axilla, thorax, abdomen and groin*. These are the nodes which carry the great share of the burden in Hodgkin's disease.

(b) In the second group are the *submucosal collections*, represented by the faucial and lingual tonsils and by the minute lymphoid follicles which are strewn through the submucosa of the gastrointestinal, respiratory and urinary tracts. They constitute an accumulation of lymphoid cells that is probably equal to, if not greater than, the numerical total of the regional collections in the neck, axilla, thorax, abdomen and groin. These submucosal lymphoid structures almost invariably escape in Hodgkin's disease.

(c) The *auxiliary lymphoid system*: In normal circumstances the auxiliary lymphoid system is represented by follicles in the walls of the arterioles of the spleen that are interposed as minute filters between the arterial blood brought to the spleen for purification and the venous blood which the spleen transfers to the liver for further detoxication. Beyond the confines of the spleen, and with the exception of the lymphoid cells in the thymus body, the auxiliary lymphoid apparatus in normal circumstances is a negligible quantity, but in certain pathological conditions, notably in Hodgkin's disease, it assumes a place of importance. Thus, in Hodgkin's disease and, incidentally, in pseudoleukemia and enteric fever, focal or streak-like collections of lymphoid cells are to be found in the walls of the portal veins. They represent hyperplasia of pre-existing lymphoid collections which are physiologically comparable to the follicles in the arterioles of the spleen, although in normal circumstances they are numerically insignificant and are functionally dormant until awakened by the necessity for additional filtration barriers between the blood of the portal and hepatic veins—an adjunct, as it were, to the defensive mechanism represented by the intervening liver lobules. In Hodgkin's disease the initial visible changes in the liver consist in the appearance of lymphoid

cells in the walls of the portal veins. In Hodgkin's disease, also, the interstitial tissues of the kidney occasionally exhibit focal collections of lymphoid cells, always in the richly vascularized cortex, in proximity to but not in the walls of the bloodvessels. Similar foci sometimes occur in the cortical substance of the kidney in enteric fever, pernicious anemia, lymphosarcoma and pseudo-leukemia. In the lungs, lying in the interstitium or in the walls of bloodvessels, collections of lymphoid cells are to be seen in various pathological conditions, and the same statement applies to the serous membranes and to the subcutaneous tissues, the bone-marrow, the interstitial tissues of the prostate, adrenal, thyroid, etc. In the thyroid they are common in exophthalmic goiter, especially in subjects of status lymphaticus. It is obvious that the follicles of the auxiliary lymphoid apparatus, although of doubtful importance in normal conditions (the spleen excepted) are susceptible of hyperplastic changes in a variety of diseases.

In Hodgkin's disease, the initial changes in the auxiliary lymphoid tissues are strictly comparable to those in the lymph nodes proper and their subsequent development, as far as it can be followed here or elsewhere, is the same. That is to say, in the auxiliary depots preliminary lymphoid hyperplasia is followed by the appearance of a connective-tissue reticulum supporting mononuclear and multinuclear giant cells with or without eosinophiles and eosinophilic myelocytes, thus completing the histological composite and bringing it into agreement with that of the larger and more ambitious lesions in other parts of the body.

In the present series, in addition to the changes in the spleen, bone-marrow and liver, the auxiliary lymphoid apparatus was concerned in 10 cases. In 1 case a solitary hyperplastic lymph node was imbedded in the submucosa of the gall-bladder and, histologically, was identical with the lymph nodes in other localities. In the same case a small nodule was present in the walls of a bronchus and, although unfortunately not submitted to microscopical examination, it was presumably of the same nature. In 3 cases nodules were present in the cortices of the kidneys and all of them showed structural alterations indistinguishable from those in the diseased lymph nodes. In 2 cases multiple nodules of characteristic histology occurred in the lungs; in another the suprarenal capsule showed microscopical foci of involvement. In 3 cases nodules were imbedded in the epicardium. In 1 of these cases there is no histological confirmation of the identity of the nodules with the lesions in other parts, although any assumption to the contrary would scarcely seem to be justified. In the other 2 cases the histology was characteristic.

Among clinicians it is a sort of tradition that Hodgkin's disease is essentially an affection of the cervical lymph nodes. This conception, however honored by repetition, is contradicted by fact.

In this series preponderating enlargement of the cervical nodes occurred once only (7 per cent). In 4 cases, or 28 per cent, the predominant enlargements occurred in the abdominal nodes, and in 6 other cases, or 43 per cent, in the nodes of the chest and abdomen in combination—a proportion of 10 to 1. In another case the liver was the most extensively involved, and in still another the spleen. In both of them the abdominal nodes were only moderately enlarged and the cervical nodes were free in 1 case, slightly enlarged in the other. In still another case the lymphoid tissues of the thymus were enormously hyperplastic and the cervical nodes were free. In other words, in 4 of the 14 cases the nodes of the neck were not involved at all (28 per cent), in 3 they were involved only to a slight extent (21 per cent) and in the remaining 6 cases they were enlarged in association with collections in the deeper parts that were proportionately far more massive.

Finally, it is a matter of anatomical interest and of clinical value that enlargement of the axillary nodes is always a direct sequence of involvement of the cervical or thoracic groups, and that inguinal adenopathy in Hodgkin's disease is sequential to involvement of the abdominal nodes. Enlargement of the axillary or inguinal nodes independently of such changes, if it exists, did not occur in this series. These facts, taken into consideration with the distribution of the lesions in the lymph nodes of the neck, thorax and abdomen, seem to substantiate the view that the provocative agent in Hodgkin's disease, whatever it may be—bacterium, filterable virus or what not—does not enter through the skin, but exclusively through mucous membranes; that it is apt to pass the first barrier of lymphoid tissues, namely, the small collections which lie in different submucosæ, without exciting any notable disturbances in them, and that it produces its greatest degree of reaction in those lymphoid structures which are situated at strategic points for purposes of filtration, namely, the lymph nodes of the neck, thorax and abdomen. In the neck, for example, enlargement of the tonsils is an infrequent prelude to disturbances in the lymph nodes of the immediate vicinity. The mediastinal nodes often attain enormous proportions without participation of the submucous lymphoid collections in the trachea and bronchi; in the abdomen the mesenteric and retroperitoneal nodes may exhibit an extraordinary degree of enlargement without changes in the solitary or agminated follicles of the intestine. In still other circumstances it appears that the provocative agent is capable of passing both the primary and secondary lines of defense; that is to say, it may filter through both the submucous follicles and the lymph nodes in the neck, thorax or abdomen, and bring about hyperplastic changes in the follicles of the spleen or in the lymphoid remains of the thymus. Moreover, Hodgkin's disease, as revealed at necropsy, not uncommonly shows a tendency to skip groups of

lymph nodes, as is shown by the combination of cervical and abdominal enlargement without participation of the nodes in the chest.

One does not have to seek far for examples of toxic lymphoid hyperplasia analogous to those encountered in Hodgkin's disease. In certain diseases of established etiology, notably tuberculosis, it is known that absorption of toxins from ulcerative lesions in the gut is capable of producing simple hyperplastic changes in the mesenteric lymph nodes without the intervention of tubercles. In a case which recently came under my observation at Bellevue Hospital, bilateral tuberculosis of the psoas magnus muscles, secondary to caseation of a vertebra, was attended by enlargement of the spleen, the organ weighing 1980 gm. and measuring 20 by 10 by 6 cm. Scattered through it were myriads of pinhead-sized yellowish foci. The retroperitoneal lymph nodes were hyperplastic to a marked degree. Microscopical examination of the spleen and of the lymph nodes revealed hyperplasia of the lymphoid follicles without a tubercle to be found in any one of numerous microscopical sections which were prepared with the object of determining this point. In typhoid fever the absorption of toxins from ulcers in the intestine is notorious as producing lymphoid hyperplasia in the mesenteric nodes, and in diphtheria simple hyperplasia of the cervical nodes is not uncommonly to be traced to absorption from the exudate in the throat.

The Liver in Hodgkin's Disease. In 10 cases of the present series (71 per cent) the liver presented foci of characteristic histology. In 8 cases nodules were visible to the naked eye, varying in size from $\frac{1}{2}$ to 2 cm. Microscopical examination showed that the nodular foci arose in the periportal spaces and were initiated by hyperplasia of the lymphoid cells in the walls of the portal veins, followed by the appearance among the lymphocytes of mononuclear and multinuclear giant cells with or without the presence of eosinophiles and eosinophilic myelocytes, the whole supported in a connective-tissue reticulum, the nodules expanding in such fashion as to subject the neighboring lobules to atrophy from pressure, but never directly infiltrating them.

In one case a huge solitary mass surrounded the portal vein shortly after it entered the liver at the transverse fissure, and appeared both to the naked eye and on microscopical examination to arise in the walls of the vein and thence to expand concentrically, pushing aside the liver tissue but not invading it. In addition, innumerable foci of microscopical size and of identical histological structure were found in the periportal connective tissues.

In Case VIII the liver was greatly enlarged. There were a few enlarged lymph nodes in the abdomen, histological examination of which showed the characteristic histology of Hodgkin's disease. Ascites was abundant. The shape of the liver was preserved in

spite of the fact that its substance was replaced to an enormous degree by fibrous bands (Fig. 1). Histologically, the changes followed the same evolution as those described in the liver in the other cases, differing, however, in the almost incredible extent to which the organ was replaced by connective tissue, due to thickening of the intrahepatic portal veins, in the walls of which microscopical examination showed the histological features of Hodgkin's disease. As far as I can learn, the extent of the changes in the liver in this case constitutes a phase in the pathology of Hodgkin's disease which has not hitherto been pointed out. The larger veins in the substance of the spleen were likewise greatly thickened and in their walls were collections of lymphoid cells and numbers of atypical giant cells. The extent of the changes in the spleen, however, was insignificant as compared with those in the liver. Nevertheless, in both of these localities the histological changes of Hodgkin's disease were found most frequently and in their most highly developed state in the walls of veins; involvement of the lymph nodes, although present, was practically negligible. I assume, therefore, that there is a variety of Hodgkin's disease in which the predominant changes occur in the lymphoid collections in the walls of veins. In this particular case the greatest degree of enlargement occurred in the liver. Perhaps it is not trespassing too far to predict that future investigation will disclose a variety of splenomegaly in Hodgkin's disease in which the size of the spleen will be shown to depend on changes in its larger veins of the same sort as those here described in the veins of the liver.

The Spleen in Hodgkin's Disease. Of the 14 cases in this series, the spleen was greatly enlarged in 9 (64 per cent). The weights recorded in 8 of the cases were 450, 500, 657, 700, 750, 840, 1220 and 1300 gm., an average of 802 gm., or 652 gm. in excess of the average weight of the spleen in health. In 8 of the 9 cases of splenomegaly, characteristic histological changes were present. In the ninth case the spleen measured 15 by 9 by 5 cm., but on microscopical examination it was found to be extensively sclerotic and the histological alterations of Hodgkin's disease were not detected, having been replaced, no doubt, by the overgrowth of connective tissue. The alternative conception that the enlargement of the spleen was due to an independent process appears to be somewhat strained. In 2 other cases the histological changes in the spleen were characteristic of Hodgkin's disease, but the organ was normal in size or only slightly enlarged and was not palpable during life. In the remaining 3 cases the spleen was normal both in size and microscopically, and was likewise not palpable during life.

Destruction of Muscle Tissues. The present study emphasizes the fact that individual skeletal muscles or groups of muscles may suffer extensive destruction by invasion of tissue of the same sort as that in the lymph nodes and elsewhere. Cunningham¹⁵ noted

similar changes in one of his cases. In one of the cases here recorded enlarged abdominal nodes were continuous with voluminous nodes in the thorax, and these, in turn, were associated with a thickened and adherent pleura on the left side and with penetration of the intercostal muscles and continue infiltration of the muscles of the corresponding pectoral region, producing a mass on this side of the chest which in size and shape resembled a miniature ham. In a second case enlarged lymph nodes in the neck were continuous with infiltration of the pectoral muscles on the right side, covering an area only slightly smaller than that of an average adult hand, and in the abdomen enlargement of the regional lymph nodes was attended by almost complete destruction of the right *psoas magnus musclē*. In a third case nodules in the skin of the right forearm were attended by continue infiltration of adjacent muscles and tendon sheaths. In all of these cases the invaded muscle tissues were subjected to microscopical examination and in all of them the histological composite of Hodgkin's disease differed in no wise from that of the lymph nodes and other tissues. .

The Bone-marrow in Hodgkin's Disease. In the present series, the bone-marrow was involved in 7 cases (50 per cent). In 1 case the marrow of all the thoracic and lumbar vertebræ was completely replaced by whitish tissue of the same sort as that in the lymph nodes, the intervertebral disks and the bony casement of the vertebral bodies remaining intact. In another case the anatomical diagnosis refers to "extensive replacement of the vertebræ," but the text of the protocol makes no mention of the part of the vertebral column involved. In this case, however, microscopical examination of the marrow showed: (a) Replacement by tissue of identical composition with that in the lymph nodes—a reticulum with lymphocytes and mononuclear and multinuclear giant cells; (b) areas of granulation tissue with innumerable thin-walled blood-vessels lying in a matrix of lymphocytes, polymorphonuclear neutrophiles, eosinophiles, eosinophilic myelocytes and red cells; (c) hyperplastic marrow, rich in cells of the sort just enumerated plus large mononuclear and myeloid giant cells. In 5 other cases the marrow spaces were occupied to a variable extent by tissue microscopically identical with that of the diseased lymph nodes. In 2 instances microscopical examination of sections from the marrow showed, in addition, numbers of giant cells with nuclei which presented all sorts of odd shapes. Morphologically identical giant cells were found in the liver in 1 of the cases, and in the lymph nodes, lungs and tonsils in another, suggesting that the giant cells had been deposited in these localities as a result of embolism from the bone-marrow.

In short, the bone-marrow in Hodgkin's disease reacts in at least two different ways: (a) It may show hyperplastic changes characterized by increase in the cells normally manufactured

there; (b) it may be replaced by tissue of identical composition with that in the diseased lymph nodes, focally or over a wide geographical range. These two types of reaction may be encountered in the bone-marrow not only in one and the same case, but in the same microscopical field.

The Nature of Hodgkin's Disease. By some pathologists, Hodgkin's disease is regarded as an infective granuloma. All attempts thus far made to establish a causal relationship between it and different microorganisms have failed. By others it is looked on as a neoplastic process. There is something to be said for and against both of these views. As a rule, tumors, excluding, of course, such growths as the teratomata, are dominated by a single type of cell or by variations of the same type, as in the mixed spindle- and giant-cell sarcomata. When tumors metastasize the secondary growths ordinarily present histological changes identical with or closely comparable to those of the parent growth, but instances are common in which it is difficult or impossible to correlate the structure of the primary growth with that of its metastases or with its continue infiltrate or its recurrent growth, or even with different parts of the parent growth, the rapid reproduction of cells, together with alterations brought about by environment, combining to produce remarkable changes in their shape and arrangement. On the other hand, the histological composite in Hodgkin's disease remains essentially the same throughout all changes of environment, in which respect it resembles an inflammatory lesion of the granulomatous type. In favor of the neoplastic nature of Hodgkin's disease, it may be advanced that the process sometimes produces continue infiltration and destruction of tissues, as has been emphasized in the present paper. On the other hand, inflammatory diseases of established etiology often pursue an equally ravenous course, notably actinomycosis, tuberculosis and the like, and, as in Hodgkin's disease, they tend to maintain their histological individuality no matter what the environment may be. Again, it may be urged that Hodgkin's disease produces circumscribed nodular lesions in different organs and that in this respect it resembles a neoplasm, but, unfortunately for this argument, inflammatory diseases may react similarly, as witness the presence of gummata in syphilis and massive solitary tubercles in the brain, together with the occasional occurrence of elevated nodules in the liver in chronic myelogenous leukemia; and yet there is no proof that myelogenous leukemia is a neoplastic process, although this, of course, is a theory that is sometimes discussed. The wide distribution of the lymph-node enlargements in certain cases of Hodgkin's disease and their immense size may be quoted in favor of the neoplastic nature of the disease, but this is offset by the observation that primary disseminated tuberculosis of the lymph nodes may pursue it as a close second. Moreover,

in Hodgkin's disease the lesions in the lymph nodes and elsewhere are made up of cells of different morphology—lymphoid and plasma cells, mononuclear and multinuclear giant cells, eosinophiles and eosinophilic myelocytes—and in order to fit into the category of metastases the secondary deposits would have to reach their new abode in the form of diversified cell collections and to proliferate as such. The alternative conception is equally fantastic, namely, that a single type of cell, when transplanted, is capable of reproducing a cell complex.

Hodgkin's disease occasionally shows spontaneous attempts at healing, as exemplified by the overgrowth and hyalinization of connective tissues, sometimes to such an extent that, in a given territory, the character of the process is completely obscured. The argument that this is in favor of the inflammatory nature of the disease is countered by the fact that in malignant tumors the overgrowth of connective tissue sometimes constitutes an equally adequate attempt at healing, as shown, for example, in scirrhous carcinomata of the breast.

It seems to me that Hodgkin's disease does not provide any criteria by which it may be grouped either among the inflammatory diseases or among the neoplasms, but that, for purposes of classification, it must be included elsewhere. Pathologists have thus far found it impossible to formulate an acceptable definition of inflammation and of neoplasia, partly for the reason that there are so many diseases which partake of the nature of both. Hodgkin's disease, I believe, is to be included in this category, together with mycosis fungoides, Cohnheim's pseudoleukemia, Sternberg's leukosarcoma, Gaucher's splenomegaly, Kaposi's lymphoderma perniciosa and a number of others. If, however, there is anything to be said in favor of one argument or the other it is that Hodgkin's disease more closely approaches an inflammatory disease in that *it maintains its histological individuality throughout all changes of environment.*

The first observable histological change in the lymph nodes in Hodgkin's disease consists in hyperplasia of lymphoid cells.¹⁶ The same statement applies to other lymphoid tissues, whether in the spleen, liver, kidney, adrenal, lung, serous membranes or elsewhere. In these localities, in the fully developed disease, the histological changes are strictly comparable to those in the lymph nodes themselves. As development proceeds the hyperplastic lymph nodes begin to lose their architectural identity, the germinal follicles disappear and the lymph cords are moulded into diffuse sheets of lymphoid cells, and at least two alien cells make their appearance to lend individuality to the microscopical picture. One of these cells is to be found in varying numbers in the lymph or blood sinuses or *lying free* among the lymphocytes or in the tissue spaces. It is a large rounded cell and is indistinguishable from the non-

granular, mononuclear cell of the normal bone-marrow. The other is larger and of identical morphology with that encountered in the normal marrow in the form of cells variously known as myeloplaxes, multinuclear myeloid giant cells, megacaryocytes and the like. In the lymph nodes, in the earlier stages of Hodgkin's disease, these myeloid giant cells *lie loose among the lymphocytes and are almost always partially or completely surrounded by a clear zone*. There is another cell which forms an important feature of the pathological-histology of Hodgkin's disease. It occurs in varying numbers in a considerable percentage of all cases—the polymorphonuclear eosinophile. In addition, there is a closely related cell which occurs in the lymph nodes in about one-third of all cases, namely, the eosinophilic myelocyte. Sometimes it is the only eosinophilic cell present; at other times it is associated with polymorphonuclear eosinophiles. In other words, *the lymph nodes and other lymphoid tissues in the fully developed Hodgkin's disease show a composite of cells, each member of which finds its prototype in the normal bone-marrow*.

In the lymph nodes of Hodgkin's disease freshly removed during life and fixed immediately in formalin or in Zenker's solution I have failed to find indications of mitotic activity in the nuclei of the lining endothelium of capillaries or lymph sinuses or other evolutionary changes in them that would account for the formation of giant cells, nor have I ever been able to trace any relationship between the giant cells and the connective tissues of the part, nor to detect any changes in the nuclei of either the mononuclear or multinuclear giant cells that appeared to me to indicate an attempt at reproduction. On several occasions, however, I have detected both mononuclear and multinuclear giant cells lying free in the lumina of capillary vessels in the enlarged lymph nodes, as if fixed in the actual process of embolism from the bone-marrow (Fig. 4). Giant cells of identical morphology with those of the normal bone-marrow have been found in film preparations of the blood in Hodgkin's disease, independently by Bunting¹⁷ and by Minot;¹⁸ and in 3 of 5 cases of Hodgkin's disease Bunting found increased numbers of megacaryocytes in microscopical sections of the bone-marrow. In my experience, I have sometimes found them in the marrow in increased numbers, indicating a response to increased demand from the peripheral tissues; in other cases I have estimated them as present in normal numbers; in still other instances I have been unable to find them in the bone-marrow at all or only to a negligible extent, in which circumstances it is probable that they had been exhausted as a result of repeated expulsion into the circulation. If megacaryocytes in Hodgkin's disease are discharged into the circulation in variable numbers and at irregular intervals, over a period of months or years, it follows that their numbers in the bone-marrow must vary, depending on the rate of discharge and

the capacity of the marrow to replenish the supply. Moreover, in Hodgkin's disease I have found atypical mononuclear and multinuclear giant cells in sections of the bone-marrow, together with identical atypical forms in the lymph nodes and other extramedullary tissues in one and the same case, which, I take it, is presumptive evidence of their derivation from the bone-marrow by the process of embolism. Flexner's observations on lymphotoxins and myelotoxins have shown that injection of these substances into certain animals is followed by hyperplasia of the lymphoid tissues and by increase in the non-granular mononuclear cells, the granular leukocytes and the multinuclear giant cells of the bone-marrow.¹⁹

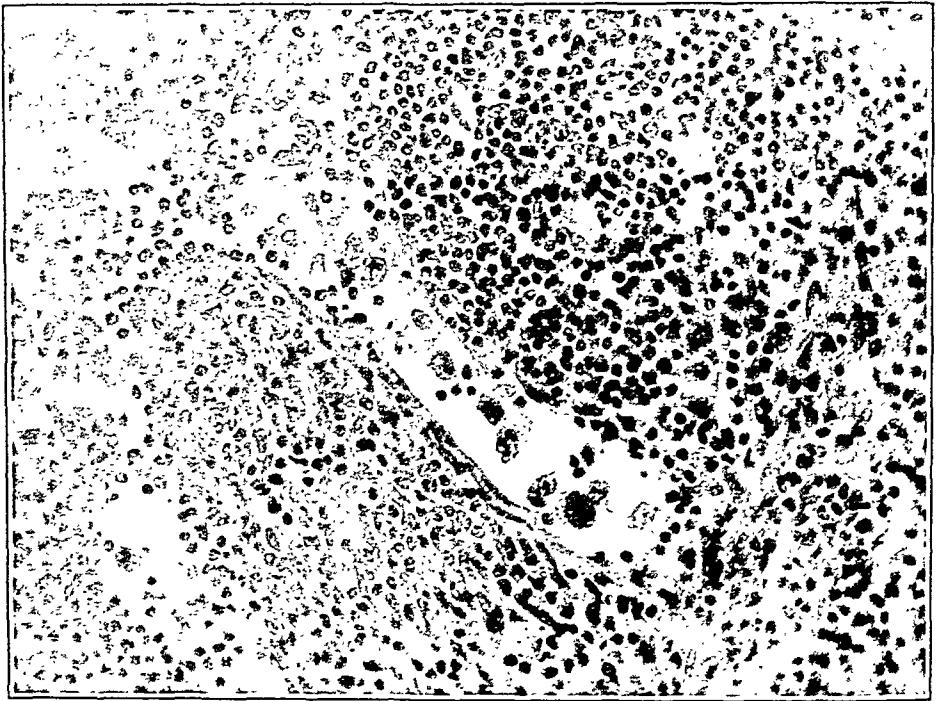


FIG. 4.—High-power photomicrograph showing mononuclear and multinuclear giant cells in the capillaries of a lymph node in Hodgkin's disease, the alien cells being derived, presumably, from the bone-marrow by the process of embolism.

Exactly similar changes occur in the same situations in Hodgkin's disease. Moreover, in chronic myelogenous leukemia the occurrence of megacaryocytes in the blood and in the spleen, liver and lymph nodes is well recognized and is commonly ascribed to embolism from the bone-marrow. If, as is sometimes claimed, the multinuclear giant cells in the lymph nodes and elsewhere in Hodgkin's disease are formed outside the bone-marrow then it may be assumed with equal reason that the corresponding cells in myelogenous leukemia are also formed beyond the bone-marrow. In these circumstances consistency demands that it be assumed that the myelocytes in the blood are manufactured outside the bone-

marrow, and, therefore, that the changes in the marrow in myelogenous leukemia are purely ornamental. I doubt if any thoughtful student of pathology would subscribe to this view. Either the megacaryocytes and myelocytes both are manufactured in the bone-marrow and are discharged into the blood, or both are products of tissue outside the marrow. Of the latter, there is no morphological proof, while the former view is supported by morphological findings and by arguments based on consecutive reasoning. That the megacaryocytes in the blood or tissues are manufactured *in situ*, and that the myelocytes in the same disease and in the same localities are derived from the bone-marrow, appears to be a still more illogical attempt to straddle an impossible situation.

I see no reason why the same argument should not be applied to Hodgkin's disease, where megacaryocytes have been identified in the blood and in the lymph nodes, liver, spleen and other tissues, together with eosinophiles and eosinophilic myelocytes; in other words, that the reaction of the bone-marrow in Hodgkin's disease and in chronic myelogenous leukemia is fundamentally the same, although the two diseases differ in the relative numbers of the cells discharged and in the reaction of the recipient tissues. In myelogenous leukemia the bone-marrow is excessively hyperplastic; myelocytes are discharged into the blood stream in enormous numbers and circulate as such; megacaryocytes are discharged in small numbers and on infrequent occasions, but nevertheless are to be found in the peripheral blood and in the bloodvessels of the deeper organs, notably in the sinusoids of the liver and in the spleen and lymph nodes. In Hodgkin's disease the bone-marrow is less richly hyperplastic; megacaryocytes are discharged in considerable numbers but at irregular and infrequent intervals. They have been found in the peripheral blood, and that they are not more commonly detected there is probably due to the fact that they circulate in small numbers and at irregular intervals. In the lymph nodes, spleen, liver and other lymphoid tissues they are to be identified in numbers—sometimes as the most prominent, although not the predominant, cell in the microscopical picture. Much the same statement applies to the large mononuclear giant cell and to the eosinophiles and eosinophilic myelocytes. In Hodgkin's disease they undoubtedly circulate, but at irregular intervals and in small numbers. Moreover, both in Hodgkin's disease and in chronic myelogenous leukemia the blood platelets have been shown to be increased in number, indicating increased activity in the marrow.

Further evidence tends to show that Hodgkin's disease and chronic myelogenous leukemia are more intimately related than is indicated by the customary text-book presentations, where it is commonly stated that in chronic myelogenous leukemia the lymph nodes do not participate at all. According to our experience at

Bellevue Hospital, this statement is erroneous. In 4 cases of myelogenous leukemia encountered at necropsy the lymph nodes in various localities were enlarged—most often in the abdomen, but occasionally in the groin and thorax, although neither in number nor in size did they begin to approach those customarily met with in Hodgkin's disease. In myelogenous leukemia and in Hodgkin's disease it appears that the provocative agent brings about changes in the lymph nodes that are qualitatively alike, but quantitatively different. In myelogenous leukemia the lymph nodes are enlarged because of simple hyperplasia of lymphoid

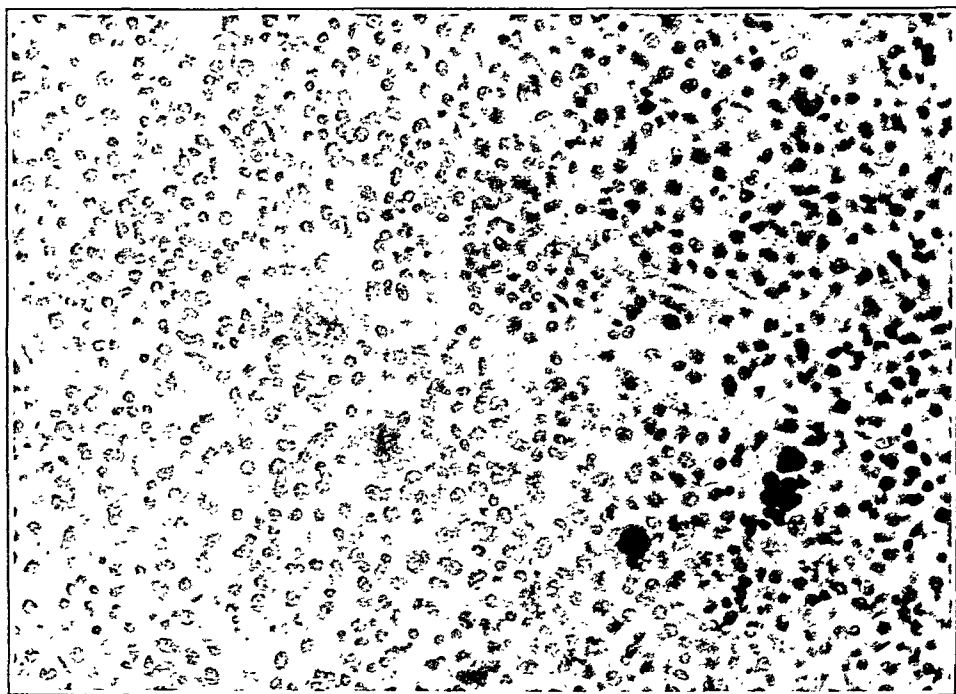


FIG. 5.—High-power photomicrograph showing mononuclear and multinuclear giant cells. From an enlarged lymph node in a case of chronic myelogenous leukemia. The histology of the lymph node is strikingly like that encountered in the same situation in Hodgkin's disease.

cells, in which respect they correspond to the smaller and more recently involved lymph nodes in Hodgkin's disease, where lymphoid hyperplasia is the predominant feature. There are instances, however, in which the lymph nodes and spleen in myelogenous leukemia might easily be mistaken, histologically, for those of Hodgkin's disease because of the presence of considerable numbers of mononuclear and multinuclear giant cells and of eosinophilic myelocytes among the hyperplastic lymphoid cells (Figs. 5 and 6). However, the histological distinction from Hodgkin's disease may be made on the ground that overgrowth of connective tissue, if it occurs, is not sufficient to obscure the architecture of the organ.

In addition, of course, the bloodvessels show vastly increased numbers of myelocytes in their lumina. In Hodgkin's disease, in the majority of cases, enlargement of the lymph nodes is excessive, but in occasional instances it does not greatly transcend that of myelogenous leukemia, as shown in several cases in this series.

It appears, therefore, that in myelogenous leukemia and Hodgkin's disease there is a certain parallelism between the reaction of the bone-marrow and of the lymph nodes and spleen which suggests that the two diseases are fundamentally related—that they are probably different quantitative responses to the same type of provocative agent.

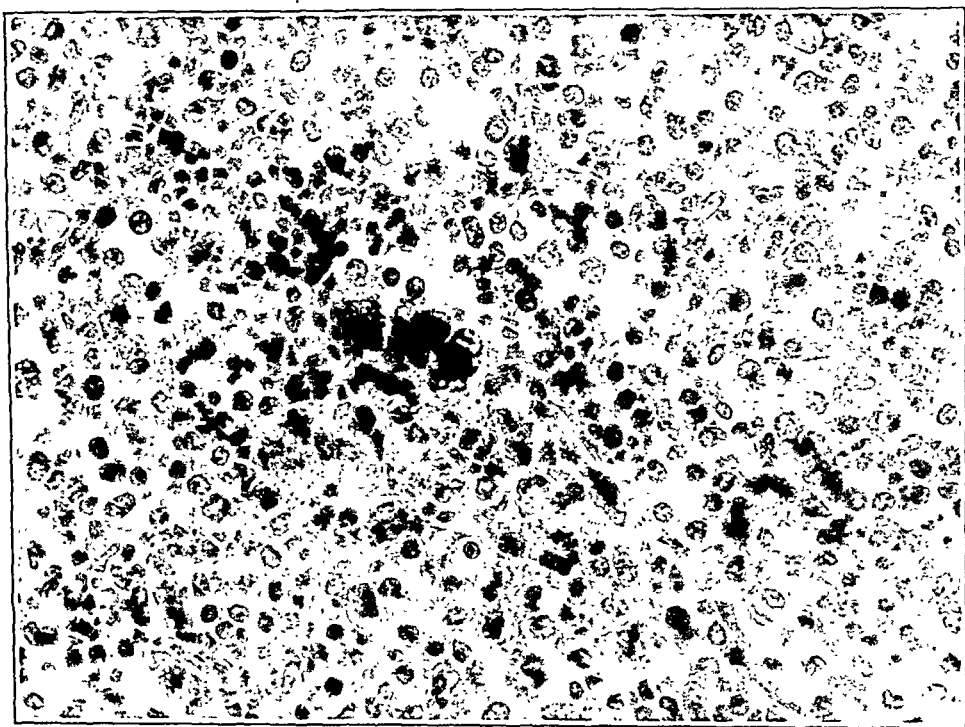


FIG. 6.—High-power photomicrograph showing multinuclear myeloid giant cells in the spleen. From a case of chronic myelogenous leukemia. Note the resemblance of the histological changes to those of Hodgkin's disease.

Symptoms and Signs, Duration, Treatment, Prognosis. *Symptoms and Signs.* Of the 14 cases in this series subjective symptoms were lacking in 5, in spite of huge lymph-node enlargements in the neck in 1, in the chest and abdomen in another and in the abdomen in the remaining 3. In another 5 cases there were complaints of pains in the abdomen or back, in association with enlarged abdominal nodes, and in 2 other cases subjective symptoms were referable to pressure on the nerve trunks of the upper extremity. In 1 instance a scalding sensation on urination was associated with pressure at the neck of the bladder. In all of the 14 cases objective signs were apparent in the form of lymph-node enlargements

in the neck, axilla or groin, emaciation, anemia, edema, changes in the skin, such as jaundice, exfoliative dermatitis and acanthosis nigricans, with or without the late appearance of such symptoms as cough and dyspnea, dependent on the pressure of enlarged lymph nodes within the thorax. The escape of fluid into various loose tissues or serous sacs was present in 10 cases (71 per cent); in the remaining 4 cases no signs of effusion were evident. Subcutaneous edema of the legs, scrotum, etc., occurred 3 times, always in company with enlargement of the intra-abdominal nodes. In 1 instance subcutaneous edema of the forearm occurred in association with invasion of the muscle tissues and tendon sheaths of the vicinity by tissue of the same sort as that encountered in the diseased lymph nodes; in a second, edema of the left pectoral region was attended by tumor-like infiltration of the muscles of the corresponding part and in a third, edema of the chest wall was present as a pressure phenomenon in Hodgkin's disease of the thymus. Involvement of the serous sacs occurred in different combinations in 10 cases, nine times as pure serous effusions and once as a purulent exudate. Ascites was noted five times, and in 4 cases was apparently due to enlargement of the intra-abdominal nodes, in the remaining case to primary involvement of the liver; bilateral hydrothorax occurred four times, twice attended by enlargement of the intrathoracic nodes and twice as a terminal event; unilateral hydrothorax was encountered twice, once accompanied by massive enlargement of the thymus. In 1 case the left pleura enclosed large collections of pus. The pleura itself was enormously thickened and in it were small composites corresponding in all histological essentials with those encountered in the same case in the lymph nodes and elsewhere—an instance of secondary involvement of a pleural membrane presenting the characteristic histology of Hodgkin's disease, and the only case in this series attended by empyema, the other effusions representing serous transudates due to interference with the venous return.

Duration. The rarity of subjective symptoms in Hodgkin's disease is of itself an interesting revelation, but the degree to which lymph-node enlargements may exist in the abdomen or thorax, or both, without giving rise to symptoms or signs of any sort until after the lapse of many months, is an astonishing illustration of the adaptability of the thoracic and abdominal viscera to gradually increasing pressure. Because of this fact it is impossible intelligently to estimate the duration of the disease. In the present series the average duration after the appearance of symptoms as related by the patients was twenty-five months—a figure which is probably of doubtful value, since historical data as related by the sick are notoriously unreliable. The shortest period was twenty days, the longest six years and two months. In 5 cases symptoms had been present for a period of three, seven (2 cases), eight and eleven

months. One case was of slightly more than a year's duration, 1 of two years' and 3 cases of over three years'. The longest case to be recorded, as far as I know, is by Cunningham, having a duration of twenty-five years.²⁰

Treatment. No method of treatment thus far devised has been shown to influence the disease favorably for more than a short time, and even in such circumstances it may be difficult to judge the effects of treatment because of the proclivity of the enlarged lymph nodes to regress spontaneously or after intercurrent infections, or without apparent reason to remain stationary for an indefinite period. Surgical intervention is hopeless and should never be undertaken except for the mechanical relief of conditions which threaten life or are intolerable. Incidentally, the removal of tissue for diagnosis is a justifiable procedure, although it should be carried out with the precautions customarily observed in surgical operations. In the groin the operation, in my opinion, should be avoided since, in this region, infection is apt to occur and to be troublesome, sometimes fatal, as in one case in this series. Spread of the disease after removal of tissue for diagnosis, if it ever occurs, is to be regarded as a coincidence. In a somewhat comprehensive experience with Hodgkin's disease, clinically and otherwise, I have yet to encounter a regrettable incident following the removal of tissue for diagnosis, with the exception of the one just mentioned. The objection that this diagnostic procedure may be followed by rapid progression is gratuitous, and is based on the assumption that cells are liberated by operative manipulation and transplanted in remote parts, whereas it is known that Hodgkin's disease is not spread by the process of metastasis, but that it has multiple foci or origin, each of which is independent of the transplantation of cells through the blood or lymph streams from one lymph node to another or from the lymph nodes to other tissues.

In recent years it has been shown that the roentgen-ray treatment of Hodgkin's disease is often followed by remarkable diminution in the size of the diseased lymph nodes, but no instance of cure by this means has thus far been recorded. As far as I am aware, there is no acceptable explanation for the changes in the lymph nodes after roentgen-ray therapy. It has been claimed that the apparently beneficent effects of the roentgen-ray are due to vascular occlusion followed by the death of cells and replacement by connective tissue. In studying tissues in Hodgkin's disease that had been subjected to roentgen-ray treatment, I have seen the vascular and necrotic changes in question, but I have also seen them in tissues that had not been treated by this method. It remains to be decided whether the reparative alterations in question are to be accredited to man's therapeutic ingenuity or to some peculiar provision that Nature makes for tissues in distress.

Prognosis. The outlook in Hodgkin's disease is hopeless.

Summary and Conclusions. 1. Hodgkin's disease is divisible into two groups of cases: (a) Those in which the changes are confined to the lymphoid structures, *i. e.*, to the lymph nodes proper and to residual lymphoid foci in the spleen, in the walls of the portal vessels and in the interstitial tissues of the lungs, kidneys, bone-marrow, subcutaneous tissues, serous membranes, etc. In fact, it may display itself in practically any tissue of the body, since minute collections of lymphoid cells are of wide distribution and, in Hodgkin's disease, lymphoid tissue is a prerequisite to development. In the present series 10 cases, or 71 per cent, belong in this group. (b) The second group of cases is attended by changes of the same sort and in the same localities as in the group just mentioned, but in addition the disease brings about continue infiltration and destruction of muscles, bloodvessels, serous and mucous membranes, erosion of bone and mechanical replacement of solid viscera. In this series 4, or 28 per cent, of the cases belong in this group.

2. It appears that we must relinquish the conception that Hodgkin's disease is most commonly shown by enlargement of the lymph nodes of the neck. In this series the disease displayed itself as an enlargement of the abdominal lymph nodes or of the abdominal and thoracic nodes in combination ten times more frequently. In the 14 cases of this series the lymph nodes of the neck were not enlarged at all in 4 (28 per cent). They were secondarily involved to a slight extent in 3 (21 per cent) and in 6 (43 per cent) they were more or less markedly enlarged, but always in association with collections in the deeper parts that were proportionately far more massive. In the remaining case (7 per cent) the cervical nodes were enormous. It is a fact of clinical value that enlargement of the axillary nodes is secondary to involvement of the thoracic or cervical nodes and that enlargement of the inguinal nodes is secondary to involvement of the abdominal nodes. These observations suggest that the provocative agent does not enter through the skin, but exclusively through mucous membranes, and probably only through the mucous membranes of the gastro-intestinal tract, although the respiratory tract cannot be excluded. It is significant, however, that in this series there was not a single case in which enlargement of the peribronchial nodes could be implicated other than as an associated phenomenon—never as the predominant focus. The brunt of attack in Hodgkin's disease is borne by the lymph nodes of the abdomen, thorax, neck, axilla and groin and by the auxiliary lymphoid system, including the spleen and liver and other residual lymphoid collections in various parts of the body; while that vast array of lymphoid follicles which lies in the submucosa of the gastro-intestinal, respiratory and urinary tracts practically always escapes intact. From this it is apparent that the provocative agent in Hodgkin's disease has a selective action on certain groups

of lymphoid tissue—a peculiarity which it shares with chronic lymphatic leukemia, in which disease the submucosal follicles are likewise apt to be spared.

3. Evidence is offered in this paper to show that Hodgkin's disease may reveal itself the most prominently in organs other than the lymph nodes—that enlargement of the spleen or the thymus or the liver may be the predominant feature, the associated lymph-node enlargements assuming a place of secondary importance.

According to our observations, Hodgkin's disease is divisible clinically and anatomically into five groups, as follows:

I. Hodgkin's disease of the regional lymph nodes:

(a) Predominant involvement of the abdominal nodes (28 per cent).

(b) Predominant involvement of the abdominal and thoracic nodes in combination (43 per cent).

(c) Predominant involvement of the nodes of the neck (7 per cent).

II. Predominant involvement of the thymus.

III. Predominant involvement of the spleen.

IV. Predominant involvement of the liver.

V. (a) Axillary involvement (sequential to cervical or thoracic lymph-node enlargements).

(b) Inguinal involvement (sequential to abdominal lymph-node enlargements).

4. In the present series the average weight of the spleen in 8 cases was 652 gm. in excess of the normal. In the ninth case the spleen was greatly enlarged, but its weight was not recorded. In the remaining 5 cases (35 per cent) the organ was normal in size or only slightly enlarged and could not be palpated during life. This latter finding is of practical application in view of the fact that palpable enlargement of the spleen is commonly regarded as a constant accompaniment of Hodgkin's disease.

In 7 cases the spleen was enlarged and nodular (50 per cent). In the remaining 7 cases no nodules were apparent in it and the shape of the organ was preserved. In this connection it is to be pointed out that the nodular condition of the spleen in Hodgkin's disease is of academic interest rather than of clinical value, since the nodules are distributed through the deeper substance of the organ and rarely, if ever, project to such an extent as to be palpable through the abdominal wall.

5. The present study emphasizes the fact that in Hodgkin's disease the skeletal muscles may be extensively destroyed by tissue of the same sort as that in the lymph nodes. In this series destructive changes are recorded in 3 cases, namely, in the intercostal and pectoral muscles in 1, in the pectorals and the psoas magnus in 1, and in the muscles of the forearm in 1.

6. The bone-marrow in Hodgkin's disease may react in at least

two different ways: (a) It may show hyperplastic changes, particularly in the eosinophiles and eosinophilic myelocytes; or (b) it may be replaced by tissue of identical composition with that of the diseased lymph nodes, sometimes over an extraordinarily wide distribution.

7. Evidence is presented in this paper which tends to show that in the reactions in the lymph nodes and in the bone-marrow there is a certain parallelism between Hodgkin's disease and chronic myelogenous leukemia. This suggests that the two diseases are fundamentally related and that they probably represent different quantitative responses to the *same type* of provocative agent.

8. Whether Hodgkin's disease is an inflammatory or a neoplastic process remains to be determined. The fact that the histological composite tends to maintain its individuality throughout all changes of environment appears to me to constitute an argument in favor of its inflammatory nature.

9. Case VIII represents a new phase in the pathology of Hodgkin's disease, marked by massive enlargement of the liver, due to structural changes in the walls of the portal vessels that are strictly comparable to the changes encountered in the lymph nodes, including the characteristic cell composite and the overgrowth of connective tissue. Similar changes were present in the same case in the walls of the larger veins of the spleen and of the medulla of the suprarenal capsule. The abdominal lymph nodes were enlarged to a negligible extent, although in them the histological changes were characteristic.

10. Cases X and XI illustrate a rare finding in the pathology of Hodgkin's disease, namely, massive thickening of the pleura with focal areas of characteristic histology.

11. From the standpoint of symptomatology, Hodgkin's disease is a striking example of the adaptability of organs to gradually increasing pressure. Enlargement of the abdominal nodes or of the abdominal and thoracic nodes in combination or of the thymus may reach remarkable proportions before giving rise to symptoms of any description, or, at worst, to complaints from the patient that are trivial in proportion to the extent of the pathological changes in his body.

12. Hodgkin's disease is an affection of the hemolytopoietic apparatus. Its histogenesis is determined: (1) By preliminary hyperplasia of lymphoid cells in various parts of the body; and (2) by the discharge of mononuclear and multinuclear giant cells from the bone-marrow, with or without eosinophiles and eosinophilic myelocytes, and their arrest by the hyperplastic lymphoid depots in pursuit of their function as filters, the fibroblastic reaction in the recipient tissues representing a mechanical process designed to support the excess of cells by which they are burdened.

BIBLIOGRAPHY.

1. Hodgkin: *Med. Chir. Trans.*, 1832, 17, 68.
2. Wilks: *Guy's Hosp. Rep.*, 1856, 2, 1865; 11, 56.
3. Sternberg: *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1899, 2, 641, 711, 770, 813, 847.
4. Symmers: *Arch. Int. Med.*, 1909, 4, 218.
5. Wade: *Jour. Med. Res.*, 1913, 29, 209.
6. Mellon: *AM. JOUR. MED. SCI.*, 1916, 151, 704.
7. Murchison: *Trans. Path. Soc.*, London, 1871, 21, 372.
8. Pel: *Berlin. klin. Wehnschr.*, 1887, 24, 644.
9. Ebstein: *Berlin. klin. Wehnschr.*, 1885, 22, 565, 837.
10. Pollitzer: *Internat. Atlas for Rare Skin Dis.*, 1891; *Jour. Am. Med. Assn.*, 1909, 53, 1369.
11. Yamasaki: *Ztschr. f. Heilk.*, 1904, 5, 269.
12. Chiari: *Centralbl. f. allg. Path.*, 1911, 22, 8.
13. Lyon: *AM. JOUR. MED. SCI.*, 1919, 158, 557.
14. Symmers: *New York Med. Jour.*, 1911, 93, 971.
15. Cunningham: *AM. JOUR. MED. SCI.*, 1915, 150, 868.
16. Symmers: *Arch. Int. Med.*, 1917, 19, 990.
17. Bunting: *Bull. Johns Hopkins Hosp.*, 1911, 22, 114.
18. Minot: *Jour. Exper. Med.*, 1922, 36, 1.
19. Flexner: *Univ. Penn. Med. Bull.*, 1902-3, 15, 287.
20. *Vide loc. cit.*

**NECROSIS AND GANGRENE OF THE URINARY BLADDER:
REVIEW OF 153 CASES, INCLUDING 19 NOT
PREVIOUSLY REPORTED.**

BY CHARLES C. WOLFERTH, M.D.,

AND

T. GRIER MILLER, M.D.,

ASSOCIATES IN MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND ASSISTANT PHYSICIANS,
UNIVERSITY HOSPITAL.

(From the Medical Division of the University Hospital and the William Pepper
Laboratory of Clinical Medicine, University of Pennsylvania.)

Introduction. Necrosis and gangrene of the urinary bladder receive scant attention or are entirely ignored in clinical and pathological text-books. This is doubtless due to the fact that so few cases have been reported, Haultain,¹ in 1890, having found records of only 56, to which O'Neil,² in 1910, was able to add 52. These authors, as well as all others who have written on this subject, have excluded from consideration those bladder affections in which, although necrosis is recognized to have occurred at some stage of the pathological process, it has been overshadowed by some other outstanding lesion. Thus the necrosis that occurs in many vesical tumors, in various ulcerative lesions and in certain extensions of inflammation from without have not been dealt with; neither has that which develops in the course of formation of fistulous com-

munications of the bladder with other organs. We also have looked upon such necrotic processes as merely incidental, and have limited our investigations to a consideration of essentially necrotic or gangrenous lesions.

Excluding the new material presented in this paper, we have been able to collect 134 acceptable cases. This figure includes 2 cases of bladder gangrene in typhoid-fever patients (an apparently rare complication) which we³ have recently reported. Since our recognition of those cases (within a year) another 1 of bladder gangrene and 2 of simple necrosis, none having any connection with typhoid fever, have been found on the medical service of this hospital and 2 others of gangrene have been studied by colleagues in another hospital, and by their permission are herein reported. In a search for more material we have examined in the laboratory of pathology of this university the records of 5250 autopsies, which were generously placed at our disposal by Prof. Allen J. Smith, and 14 additional cases have been found, 4 of which were diagnosed gangrene and 10, necrosis.

In view of this amount of previously unreported material (19 cases) which we have been able to assemble, it appears to us that necrosis and gangrene of the bladder are less rare than is indicated by the literature, and that the subject has not received the attention, either from clinicians or pathologists, that its importance warrants. Furthermore, many of the problems surrounding this highly interesting condition are still obscure. It has seemed worth while, therefore, to record the observations on our 3 recent cases and on 2 from the service of Dr. George Wilson at the Episcopal Hospital of Philadelphia, to present certain data on the material supplied by the pathological records of this medical school (see Appendix), to attempt a classification of all the available cases on the basis of the outstanding clinical conditions with which they have been associated and to discuss briefly various clinical and pathological aspects of the affection.

Nomenclature. The cases have been described under a great variety of names, including "gangrene of the bladder," "gangrenous cystitis," "exfoliation of the bladder," "exfoliative cystitis," "exfoliative necrosis of the bladder," "necrotic cystitis," "membranous cystitis" and a number of others. Some have been incorrectly designated "croupous," "diphtheritic" or "pseudomembranous cystitis."

The essential feature in all is death of bladder tissue *en masse*, or in other words, necrosis. Consequently, if all the cases are to be included under one name they should be called "necrosis of the bladder," as suggested by Haultain. In most instances, however, the dreadful feter of the urine and the obvious putrefaction of the destroyed bladder tissue leave no doubt as to the presence of true gangrene. It may be that the gangrene is merely a secondary

change in necrotic bladder tissue, but to designate such a condition as "necrosis of the bladder" when gangrene is present is surely inadequate. For this reason we have preferred to retain in addition the name "gangrene of the bladder" for those cases to which it is clearly applicable—not in any attempt radically to differentiate gangrene from simple necrosis, but in order to draw attention to the characteristic and striking clinical features of the former group of cases.

"Exfoliative cystitis" and "exfoliation of the bladder" should be dropped from the nomenclature. Exfoliation of the dead tissue may be expected always to occur if the patient recovers or the illness is sufficiently protracted, but it is merely an incidental, although sometimes a spectacular, occurrence in the course of the disease. Such designations, moreover, give no scientific idea as to the nature of the lesion.

Review of the Literature. Attention was first attracted to necrotic or gangrenous lesions of the bladder by the passage of exfoliated tissue *per urethram*. Large fragments or even complete casts of the bladder not infrequently have been extruded. According to Haultain,¹ the earliest writers to mention exfoliation of the bladder were Willius (1650), Ruysch and Morgagni. Tulpius,⁴ in 1715, reported a case in which a membrane was passed with crystals adherent to it. These early writers all believed the exfoliated material to be bladder tissue, but Fontaine⁵ (1815) and Andral⁶ (1829) contended that it was false membrane. Finally, in a case of Lever's⁷ (1852) the exfoliated membrane was examined microscopically by Gull, who demonstrated that bladder tissue was present. This finding has since been confirmed in many other cases. It has likewise been shown that false membrane containing no bladder tissue may be exfoliated and passed *per urethram*, and such exfoliated material usually has been called "pseudo-membranous," "diphtheritic" or "croupous." Guyon⁸ eventually clearly differentiated these two conditions as separate entities, and his opinion has been generally accepted. Aschoff,⁹ however, states that there is a variable amount of necrosis of the bladder wall even in diphtheritic cystitis. The relationships of these conditions will be discussed later.

Much has been written regarding the etiology of the condition, and this also will be referred to under the appropriate heading, but it is proper to say here that neither clinical observations nor experimental methods have as yet led to any unanimity of opinion or to any well-established facts regarding this phase of the subject. This is perhaps partly due to the fact that the available information regarding its pathological-histology is limited largely to that obtained from examinations of exfoliated materials and to a few brief descriptions of the microscopical appearance of the bladder walls. It is also in part due to the scarcity of data on the bacteri-

ology of the condition, especially in its early stages. On the other hand, the clinical course of the disease, the symptoms and the character of the urine have been fully and carefully described in many cases, even by the earlier writers, so that there is a great deal of data and more or less uniformity of opinion on these subjects.

On the whole it may be said that very little progress has been made in our knowledge of necrosis or gangrene of the bladder since Haultain's¹ review of the subject in 1890.

Report of Cases (Five in Number). *CASE I.—Gangrene of Bladder.* M. K., white, female, aged fifty-five years, was admitted to the medical division of the University Hospital on September 28, 1922, on account of pain in the lower abdomen and inability to void urine. She was semistuporous, answering simple questions with difficulty, so that it was necessary to obtain the history from her husband. He stated that she had fallen and injured her head four or five years previously, and had not been mentally clear since. For three or four years she had had frequency of urination and occasional retention, but the trouble had always passed off without medical treatment. The attack which brought her to the hospital began three weeks before her admission and was characterized by pain in the lower abdomen, becoming more and more severe, and some abdominal enlargement.

On admission the temperature was 99.8° F., the pulse-rate 120 and the respiratory frequency 28. The pulse was of very poor quality and the blood-pressure 95/75. The left pupil was larger than the right, but both were regular and reacted to light. The lips were dry and sordes were present. The tongue was dry and beefy in appearance. Examination of the thorax was negative. The lower abdomen was greatly enlarged, tense and tender on pressure.

She was immediately catheterized by a nurse but only a small amount of urine was obtained. Shortly afterward the resident physician was more successful, obtaining 2100 cc of bloody, alkaline urine, and at the end a large amount of thick pus. The passage of the catheter was easy but very painful, apparently on account of inflammation and excoriation about the urethra. A pelvic examination showed the uterus to be small and in ante-position. There were no adnexal masses palpated.

During the next few days catheterization and irrigation of the bladder were performed frequently, and, although the urine remained bloody and contained a large amount of pus, there appeared to be some clinical improvement. The pulse became stronger, the blood-pressure rose to 110/60 and she was less dull mentally. The temperature varied between 97 and 99.6° F. and the pulse between 85 and 120. On October 4 she voided 300 cc of urine voluntarily and one specimen was reported acid in reaction.

On October 5 a cystoscopical examination by Dr. Floyd E. Keene was reported upon as follows: "Bladder capacity, 240 cc. The whole dome of the bladder presents a shaggy gangrenous mucosa. The bladder base presents large areas of fibrino-purulent deposit with here and there areas of intense redness which represent either a cystitis or areas of exfoliated mucosa. Because of the diffuse coating of the bladder base, it is impossible to define accurately the underlying lesion, but examination *per vagina* discloses intense induration of the bladder base, and the underlying lesion is, in all probability, malignant."

The urinary output was good, never falling below 1100 cc per day. The highest specific gravity was 1022. All but one specimen were alkaline, all were reddish to dark red in color, due to the presence of blood, and pus was abundant. The urine was fetid for several days after admission, then the odor became merely ammoniacal until two days before death, when it again became fetid. Numerous small grayish-white fragments were passed through the catheter, none of those observed being more than 1 or 1.5 cm. in length. Many of these fragments were examined for bladder tissue, but all were negative. They consisted principally of pus cells with a slight admixture of erythrocytes.

Microorganisms were abundant in the urine constantly. Aërobic cultures showed principally hemolytic streptococci and a member of the proteus group. Anaërobic cultures were negative for *Bacillus neigeux* and other anaërobic organisms of this type.

On admission the leukocyte count was 20,200 with 83 per cent of polymorphonuclear cells. There were 4,100,000 erythrocytes and 74 per cent of hemoglobin. The leukocyte count rose steadily and the last one, made on October 6, was 41,200. The blood and spinal-fluid Wassermann reactions were negative. The cell count and the colloidal-gold curve of the spinal fluid were also negative. The blood-urea nitrogen on September 30 was 50 mg. per 100 cc and on October 6, 30 mg.

Death occurred October 9, and although no autopsy was permitted a digital exploration of the bladder was made. The wall appeared to be uniformly thickened, and there were no localized areas of induration or masses of any kind. It was friable and easily ruptured by the finger. Several fragments were withdrawn for microscopical examination. These showed the wall to be nearly 1 cm. in thickness. The tissue was foul-smelling and the inner surface gangrenous in appearance. There was no evidence of inflammation on the exterior surface.

A *microscopical section* showed that there was present some normal epithelium, the continuity of which was broken in places and in its stead there was an irregular mass of tissue consisting of debris, small round cells, polymorphonuclear cells and blood. This necrosis did not extend very deeply into the submucosa.

The submucous layer was greatly thickened, showing an overgrowth of young fibrous connective tissue with a moderate degree of infiltration of small round cells and congestion of the blood-vessels in certain areas. In one or two places there was marked infiltration of small round cells and there were also some scattered giant cells with three to four nuclei in each. The muscular layers were intact and of normal thickness. The cells and fibers stained clearly and showed no degeneration. Between the fibers there was a slight increase in small round cells. The interfibrous coat was of average thickness and showed no abnormal changes.

Comment. Both the history of this patient and the histopathology of the bladder point to a cystitis much older than the acute condition which brought her to the hospital. The etiology of this chronic cystitis could not be determined. The development of gangrene was undoubtedly contributed to by the occurrence of extreme urinary retention in a bladder that was almost certainly already the seat of infection. No evidence could be obtained to support the recent contention of Legueu that *Bacillus neigeux* is responsible for gangrene of the bladder, although several special cultures were made in an effort to recover this or other anaërobic organisms.

CASE II.—W. P. C., white, male, a fireman, aged sixty-seven years, was admitted to the service of Dr. George Wilson at the Episcopal Hospital of Philadelphia (reported through the courtesy of Dr. Wilson and Dr. C. Y. White, the pathologist) on January 15, 1923, because of weakness and difficulty in passing his urine. He had been confined to bed for four days before admission. In August, 1922, he had suffered from an apoplectic attack which affected his left leg only.

Physical examination revealed good general development and nutrition, some emphysema, left-sided cardiac enlargement with a systolic murmur and urinary bladder distention, which necessitated catheterization. He soon developed a numbness in his right leg with disability and incontinence of feces.

A *neurological examination* on January 20 by Dr. Wilson showed a complete paraplegia, with typical positive bilateral Babinski reflexes and absent deep tendon reflexes. On January 27 bloody alkaline urine was obtained *per catheter*, and some shreds were observed. There was considerable pain and distress in the bladder area. At this time a cystoscopical examination revealed what was considered a sloughing malignant lesion of the bladder wall. It was believed that there had occurred from this metastasis to the vertebræ.

The patient died on February 4, and necropsy showed a carcinoma of the prostate and of the vertebræ, but only ulceration and gangrene of the bladder wall itself, with coils of intestine adherent

to the fundus of the bladder. The contents of the bladder were greenish, purulent and of foul odor. The mucous membrane was entirely destroyed and the wall was friable throughout.

The *microscopical sections* were reported upon as follows: Prostate shows malignant adenoma, papillary in places. The bladder wall may be described as the seat of two distinct processes. The muscular layer shows fibrosis and chronic progressive inflammation with involvement of the muscle bundles, some of which are changed into fibrous bands, others show granular degeneration and vacuolization, while some of the muscle groups are normal. Internal to the muscular layer is a thin zone of granulation tissue upon which lies a polymorphonuclear zone, internal to which the tissue is completely necrotic. Arterioles and capillaries remain patent up to the zone of granulation tissue. Some small thrombotic veins, however, can be found in this area. In none of the sections is there evidence of extension from the tumor in the prostate.

Diagnosis. Chronic fibrous inflammation of the outer layers of the bladder wall; acute, purulent and necrotizing processes internal to this.

Comment. This case also illustrates the difficulty of differentiating gangrene from carcinoma of the bladder, even when cystoscopic study is made. Three possible factors exist for the production of the gangrene: Urinary retention, a central nervous system lesion and infection.

CASE III.—A. C., female, white, aged forty-seven years, was admitted to the service of Dr. George Wilson at the Episcopal Hospital (reported through the courtesy of Dr. Wilson and Dr. C. Y. White) on December 6, 1922, on account of pain in the back and inability to move her legs. In the preceding September she had struck her leg against a table, and two days later an inflammatory lesion requiring incision was recognized. At about this time there had developed a knife-like pain around her waist. Three days before her admission she became unable to move her legs, this paralysis having come on gradually and with much pain. For these three days also she had been unable to void urine voluntarily and had been catheterized. There was no incontinence of urine. On admission she complained mainly of some numbness in the legs.

Examination revealed an obese woman, with a flaccid paraplegia and some general pallor of the skin and mucous membranes. The right pupil was larger than the left and irregular and the tonsils were diseased. The plantar and patellar reflexes were absent. The abdominal reflexes were lost. There was some disturbance of the pain and temperature sense in the right lower extremity. The sense of position was intact in both great toes. There was generalized abdominal tenderness with angulation at about the

sixth dorsal vertebra, and a roentgen-ray showed absorption of the bodies of the fifth and sixth thoracic vertebræ. The urine showed a low specific gravity, a trace of albumin and occasional light and dark granular casts, but only a few leukocytes, though no examinations were recorded after December 7. She died on December 15.

Autopsy revealed a neoplasm of the vertebræ and gangrenous cystitis. The bladder wall was thickened, the mucous membrane gangrenous and the urine purulent.

Microscopical sections of the bladder wall were reported upon as follows: The inner layer is fibrinous with an infiltrate of polymorphonuclear cells. It is necrotic, but there is no massive slough present in the sections examined. Cellular infiltrate and some fibrin may be seen between the muscle bundles, some of which have been partly destroyed. About the middle of the bladder wall bloodvessels are quite numerous, in some places having well-developed walls associated with considerable amount of connective tissue. This suggests that chronic inflammation had existed prior to the recent necrotizing processes. Small hemorrhages may also be found in the muscular layer. Beneath the fibrous layer there is also a recent fibrino-cellular change. The process seems like a severe acute necrotizing one, fairly well distributed through all layers of the bladder wall.

Comment. There was nothing elicited in the clinical study to account for the histological evidences of chronic inflammation of the bladder. Cystitis may have occurred during the period of illness prior to paralysis and acute retention. The chronic inflammation of the bladder presented a favorable soil for the development of an acute necrotizing process following retention and catheterization. Thus, as in Case II, there are three possible factors in the production of the bladder lesions: Retention, infection and central nervous system disease.

CASE IV.—*Necrosis of Bladder.* Mrs. E. K., white, married, aged seventy-two years, was admitted to the medical division of the University Hospital, May 28, 1922, and died two days later. The patient was so ill that no history could be obtained beyond the fact that she had been short of breath for about a year and had been told by her physician that she had diabetes. The physical examination showed signs of extreme cardiac failure. There were marked dyspnea, cyanosis and edema, a large effusion in the right chest and a greatly enlarged liver. The heart area was greatly increased and auricular fibrillation was present. There was advanced arteriosclerosis of the radial, brachial and retinal vessels. The blood count was normal and the blood Wassermann test negative. The blood sugar was 0.273 per cent.

Only one urine specimen was obtained. It was amber, contained a flocculent sediment, had a specific gravity of 1.029, was acid and

showed a cloud of albumin and some sugar, but was negative for acetone.

Microscopically, it revealed a few narrow hyaline, light granular and epithelial casts, no mucus, no erythrocytes, 85 to 100 leukocytes per high-power field, a few epithelial cells and no crystals.

The right chest was tapped and 400 cc of fluid removed, but this did not bring about any improvement. Death appeared to be due to heart failure.

Autopsy showed advanced aortic sclerosis with ulceration; cardiac hypertrophy; coronary arteriosclerosis; beginning cardiac aneurysm; terminal congestion and edema of the lungs; lobular pneumonia in the right lower lobe; sclerotic changes in the spleen, kidneys, pancreas and liver.

The urinary bladder was normal in size. The inner aspect of the wall was here and there definitely reddened and in a few places there were necrotic areas, greenish-red in color and averaging several millimeters in diameter. The rest of the inner wall, however, was gray, entirely unbroken and almost normal in appearance.

On microscopical examination, the mucosa was found completely destroyed in two sections of the necrotic areas examined, and replaced by a fibrino-cellular exudate. The fibrin occurred in the form of broad strands, rather than as a fine network. The submucosa and even part of the muscularis were likewise destroyed and replaced by similar foreign material. The portion of muscularis which was left presented a moderate separation of the poorly staining swollen muscle fibers. The serosa was normal.

Comment. The only antemortem finding that could be regarded as pointing toward an affection of the bladder in this case was the excess of leukocytes in the urine, but on account of the desperate condition of the patient symptoms may have been masked. There was, however, no retention. The necrosis obviously was in a very early stage and what its eventual outcome might have been, had the patient lived longer, may only be conjectured. The condition was of pathological, rather than clinical interest.

CASE V.—Mrs. S. L., white, a widow, aged forty-three years, was admitted to the medical division of the University Hospital, August 25, 1922, in an advanced stage of cardio-vascular-renal disease. There was tremendous cardiac enlargement, passive congestion of viscera and edema of dependent parts of the body. A hard nodular mass palpated in the right hypochondrium, was thought to be a diseased gall-bladder. The systolic blood-pressure was consistently above 200 and the diastolic varied between 120 and 140. Examinations of the urine and the results of kidney function tests indicated advanced renal insufficiency. The patient showed no response to treatment and the evidences of cardiac failure and renal insuffi-

ciency increased. During the last few weeks of life large abscesses developed in various parts of the body. Urine examinations were made routinely and showed no excess of leukocytes until three days before death (which occurred on November 10), when they were reported as numerous. The final specimen was acid in reaction and no red cells were found. No symptoms referable to the bladder were noted, but this may have been due to the fact that the patient was irrational for several days before death.

Autopsy performed four hours after death showed widespread arteriosclerosis, marked cardiac hypertrophy and coronary sclerosis, chronic glomerular and tubular nephritis, gall stones and empyema of the gall-bladder. The urinary bladder was normal in size. The mucosa was exceedingly reddened and the submucous vessels greatly congested. Near the urethral opening there were several superficial frankly necrotic areas varying from 5 mm. to 2 cm. in diameter. The lesions were pale, dirty gray and rough in appearance and the edges were slightly raised.

Comment. This case in its clinical and pathological aspect resembles Case IV.

Etiology. Various causes have been assigned for the development of necrosis and gangrene of the bladder wall, but no particular one of them seems satisfactory for all the cases. Cossy¹⁰ (1843), analyzing various possible factors for the production of this complication in his series of typhoid-fever patients, concluded that the gangrene which he described was due to some unknown but inherent characteristic of the particular epidemic which he encountered. Haultain¹ (1890) believed that deficient nutrition was the basal factor, this resulting from mere urinary retention in some cases (interfering with the venous circulation) and in others from outside pressure on the neck of the bladder (labor and impacted pelvic masses). O'Neil² (1910) adhered to Haultain's theory, but in addition called attention to a group that could be explained only by infection, while Mock¹¹ (1911) and others (see Table VII) report cases in which chemical irritants were obviously of etiological significance. Cathelin² (1919) emphasized the primary importance of some central nervous system lesion and looked upon retention, catheterization, irritants, etc., as only secondary factors. Pepin,¹³ Legueu¹⁴ and Economos¹⁵ have championed the infectious theory; Legueu insisting that only certain anaërobic organisms were causative.

Experimental necrosis of the bladder has been produced by May¹⁶ and by Heubner.¹⁷ The former showed that continuous artificial urinary retention in dogs until death (sixty hours in two experiments) produced extensive hémorrhage in the bladder wall and separation of the mucosa and submucosa at the fundus by extravasation. When retention was produced intermittently the mucosa and submucosa were broken down and filled with granular

material. Heubner ligated the neck of the bladder in rabbits, thus obstructing the arterial supply, for periods as short as two hours and then allowed the circulation to resume. The animals were killed at various intervals thereafter, from within a few hours to five or six days, and necrosis of the bladder was found. He concluded that even temporary disturbance of bladder circulation could bring about necrosis. These experiments of May and of Heubner have been cited frequently in support of the view that mechanical disturbance rather than infection is the important etiological factor.

In an attempt to make use of our collected data for the elucidation of this problem we have assembled the cases, insofar as possible, in accordance with the presence and apparent importance of certain outstanding clinical features. For instance, in Table I are grouped all the cases reported in women who were pregnant and who had retrodisplaced uteri. It will be seen that all of these had retention, due in the main to outside pressure, and that many of them had been catheterized. It is probable that in all of them, though it is not so stated in the reports, catheterization had been performed, thus affording in addition an opportunity for infection. Among the 21 labor cases (Table II) only 15 are reported as having had retention, but pressure on the neck of the bladder was a possible factor in all. It was these cases together with those under Table III (pelvic masses), in 3 of which it is stated that retention did not occur, that originally led Haultain to the belief that gangrene might develop not only from retention but also as a result of pressure on the neck of the bladder, shutting off the arterial circulation.

In Table IV (cystitis) there is clear evidence of a bladder infection. In Table V (stricture of urethra) 6 of the 7 cases had retention and possibly the seventh did also, though it is not so stated. It may be safely assumed, furthermore, that all these were catheterized, and as well those of Table VI (stone in bladder). The etiological significance in Table VII of the irritants injected cannot be doubted. Of those cases occurring in patients with typhoid fever, pneumonia and acute malignant endocarditis (Table VIII) 6 are reported to have had urinary retention, while 2 did not. In this table blood infection would seem to have been a possibility. Central nervous system lesions (Table IX), as is well known, do frequently give rise to trophic disturbances, but they also often give rise to urinary retention; and in view of the small number of such bladder disturbances in comparison with the large number of central nervous system lesions, even with retention, it is perhaps fair to assume that the trophic influence is not the primary cause. This is especially true since it cannot be invoked to explain the many other necrotic and gangrenous bladder cases. Trauma (Table X) may readily give rise to retention and subsequent catheterization with infection, or it may involve actual penetration of

the tissues (even the bladder itself) from the outside, thus more directly bringing about an infective condition. Various of these factors may have been operative in our miscellaneous group (Table XI).

TABLE I.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN PREGNANT WOMEN WITH RETRODISPLACEMENT OF THE UTERUS.

Author	Reference.	Age.	Urinary retention.	Catheterized.	Character of urine.*	Exfoliation.	Depth of the lesion.†	Result.‡
1. Van Doeberen	Observat. Acad. Groningæ, 1765, p. 83	20	+	0	B	+	Per.	D
2. Lynne	Med. Observat. and Enquir., 1771, 5, 388	40	+	+	..	+	..	D
3. Naumberg	Stark's Arch., 1796, 6, 381	34	+	0	B	+	..	D
4. Saxtorph	Gesammelte Abhandlungen, 1803, 1, 261	..	+	+	..	D
5. Zeitfuchs	Seibolds Jahrb. f. Geburtsh., 1833-1834, 13, 99	33	+	+	BPA	+	1	L
6. Kiwisch Ritter von Rotterau	Vrtljschr. f. Heilkunde, 1844, 2, 37	28	+	+	BP	+	1	L
7. Wittich	Neue Ztschr. f. Geburtsh., 1847, 23, 98	28	+	..	BP	+	3	L
8. Luschka	Virchow's Arch. f. path. Anat., 1854, 7, 30	26	+	+	..	+	2	D
9. Rosenplanter	Quoted from Haultain, Inaugural Dissertation, Dorpat, 1856	..	+	+	2	L
10. Bamberger	Thésis, Paris, 1860, p. 64	..	+	D
11. Dray	Quoted from Haultain, Med. and Phys. Jour., 1860, p. 456	..	+	D
12. May	Inaugural Dissertation, Giessen, 1862	..	+	+	2	D
13. Haussmann	Monatsschr. f. Geburtsh., 1868, 31, 132	39	+	+	FA	+	1	L
14. Schatz	Arch. f. Gynäk., 1870, 1, 469	35	+	..	PF	+	3	D
15. Southey	Lancet, 1871, 1, 610	16	+	+	FA	+	4	D
16. Godson	Brit. Med. Jour., 1871, 2, 432	26	+	+	BFA	+	4	L
17. Wardell	Brit. Med. Jour., 1871, 1, 613	28	+	..	F	+	1	L
18. Gervis	Obst. Trans., 1874, 16, 233	33	+	+	BF	D
19. Gervis	Obst. Trans., 1874, 16, 233	36	+	+	B	D
20. Moldenhauer	Arch. f. Gynäk., 1874, 6, 108	33	+	..	BFA	+	3	D
21. Williams	Obst. Trans., 1874, p. 258	..	+	+	1	D
22. Brandeis	Arch. f. Gynäk., 1875, 7, 189	36	+	..	BFA	+	1	L
23. Frankenhauser	Arch. f. Gynäk., 1877	39	+	+	BPF	+	4	L
24. Madurowicz	Wien. med. Wchnschr., 1877, p. 2167	27	+	..	BPFA	+	4	L
25. Veit	Samml. klin. Vortr., Leipzig, 1879	..	+	+	1	D
26. Veit	Samml. klin. Vortr., Leipzig, 1879	40	+	..	BPF	+	1	L
27. Kleim	Inaugural Dissertation, Berlin, 1880	33	+	..	BPFA	+	3	D
28. Moreau	Quoted from Haultain.	..	+	Per.	4
29. Krukenberg	Arch. f. Gynäk., 1882, 19, 261	33	+	..	PFA	+	4	D
30. Walters	Obst. Trans., London, 1883, 25, 33	..	+	+	1	L
31. Valenta	Memorabilien, 1883, 28, 1	..	+	+	F	+	Per.	4
32. Hurry	Edinburgh Jour., 1884, 29, 1000	34	+	..	BPA	+	2	D
33. Pinard	Ann. de gynéc. et d'obst., 1886, 26, 338	21	+	..	BPFA	+	3	D
34. Corkhill	Lancet, 1887, 2, 1311	28	+	..	BPFA	+	..	L
35. Hartmann	Bull. Soc. anat. de Paris, 1888, 63, 518	21	+	..	BPFA	+	3	D
36. Rasch	Tr. Obst. Soc., London, 1889, 31, 129	..	+	..	B	D
37. Haultain	Rep. Lab. Roy. Coll. Phys., Edinburgh, 1890, 11, 185	26	+	..	BF	+	4	D
38. Haultain	Rep. Lab. Roy. Coll. Phys., Edinburgh, 1890, 11, 185	43	+	..	BF	..	2	D
39. Oliver	Lancet, 1890, 1, 638	..	+	..	F	..	4	D
40. Cockram	Med. News, 1893, 63, 633	30	+	..	BF	+	1	L

Footnotes (applicable to all the tables).

* "B" indicates bloody; "P," purulent; "F," fetid; "A," alkaline.

† "1" represents involvement of the mucosa only; "2," of the mucosa and submucosa; "3," of mucosa, submucosa and muscular layer; "4," of the entire bladder wall; "Per" represents perforation of bladder wall.

‡ "D" represents death and "L" recovery.

TABLE II.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER DEVELOPING IN WOMEN AFTER LABOR.

Author.	Reference.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of the lesion.	Result.
1. Hunter . . .	Med. Observ. and Enquir., 1771, 4, 58	38	+	+	B	+	..	D
2. Barnes . . .	Med. Times, 1861, 1, 186	..	+	+	BF	+	1	L
3. Hewitt . . .	Quoted from Hautain, Med. Times and Gaz., 1863, 11, 522	+	..	L
4. Martyn . . .	Path. Trans., London, 1863, 15, 137	40	+	+	PFA	+	3	L
5. Wells . . .	Med. Times and Gaz., 1863, 15, 140	22	+	+	BA	+	3	D
6. Wells . . .	Med. Times and Gaz., 1863, 15, 140	..	+	+	BPA	+	4	L
7. Whitehead . .	Brit. Med. Jour., 1871, 2, 432	..	+	+	..	+	1	L
8. Phillips . . .	Brit. Med. Jour., 1871, 1, 662	21	+	+	..	+	2	L
9. Bell . . .	Edinburgh Med. Jour., 1875, 20, 935	+	1	L
10. Maurer . . .	Inaug. Dissertation, Berlin, 1880	31	+	+	BPFA	+	2	L
11. Doran . . .	Obst. Trans., London, 1881, 23, 2	31	+	+	BA	+	3	L
12. Ribnikar . . .	Inaug. Dissertation, Zurich, 1882	36	+	+	1	D
13. Otis . . .	Boston Med. and Surg. Jour., 1883, 31, 458	26	+	+	BFA	+	2	L
14. Aveling . . .	Obst. Trans., London, 1883, 25, 33	..	+	+	BF	+	1	L
15. Boldt . . .	Am. Jour. Obst., 1888, 21, 350	18	?	+	BPFA	+	3	D
16. Favell . . .	Lancet, 1900, 2, 1352	+	1	D
17. Stoeckel . . .	Monatsschr. f. Urol., 1902, 7, 201	0	BPF	+	2	L
18. Arroyo . . .	Quoted from O'Neil	25	+	+	F	+	2	L
19. O'Neil . . .	Surg., Gynec. and Obst., 1910, 10, 503	33	+	+	B	+	..	L
20. O'Neil . . .	Surg., Gynec. and Obst., loc. cit.	30	+	+	FPB	+	..	L
21. Adrian . . .	Deutsch. med. Wehnschr., 1910, 36, 1585	32	+	+	BP	+	3	L

TABLE III.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WOMEN WHO SUFFERED FROM EXTERNAL PRESSURE ON THE URINARY APPARATUS, EXCLUSIVE OF THOSE REFERRED TO IN TABLES I AND II.

Author.	Reference.	Age.	Retention.	Catheterized.	Condition giving rise to pressure.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Litzmann	Arch. f. Gynäk., 1880, 16, 323	35	+	+	Extrauterine pregnancy	B	..	4	D	Perforation of bladder.
2. Lohlein .	Ztschr. f. Gebirsh. u. Gynäk., 1888, 14, 534	36	+	+	Uterine fibroid; operated	BPFA	..	2	D	Operation possible cause.
3. Haas. . .	München. med. Wehnschr., 1889, 36, 401	..	0	0	Vaginal tampon	BP	+	2	L	Tampon inserted after abortion.
4. Southam	Med. Chron., Manchester, 1892, 17, 230	42	0	..	Pessary	BPFA	+	3	L	Cystitis preceded gangrene.
5. Gottberg	Inaug. Dissertation, Marburg, 1892	18	+	+	Hematometra	A	+	2	L	Operated on.
6. Gottberg	Inaug. Dissertation, Marburg, 1892	42	+	+	Myoma uteri	BF	+	..	L	Trauma; was thrown from sleigh.
7. Vahle . .	Inaug. Dissertation, Marburg, 1899	48	+	+	Incarcerated myoma uteri	P	..	3	D	
8. Plaut . .	Inaug. Dissertation, Marburg, 1899	Extrauterine pregnancy	D	Peritonitis, sepsis.
9. Stoeckel	Monatsschr. f. Urol., 1902, 7, 201	32	Vaginal tampon for the bleeding	BPF bac.	+	2	L	Late pregnancy; vesico-vaginal fistula developed.
10. Barlet .	Brit. Med. Jour., 1912, 1, 122	26	0	0	Vaginal tampon	BP acid	+	3	L	Late pregnancy.
11. Wernitz .	Gynäk. Rundschau., 1912, 6, 208	19	+	+	Hematocolpos	BPFA	+	3	L	

TABLE IV.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH CYSTITIS WAS THE ONLY DISCOVERABLE CONDITION OF PROBABLE ETIOLOGICAL SIGNIFICANCE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Lever . .	Guy's Hosp. Rep., 1853, 8, 49	F	28	+	..	PF	+	3	L	"Nervous shock."
2. Buchanan .	Brit. Med. Jour., 1871, 2, 520	M	60	+	+	PA	+	1	L	
3. Kermisson .	Bull. Soc. anat. de Par., 1875, 10, 291	M	55	PA	+	2	D	
4. Dubard . .	Bull. Soc. anat. de Par., 1877, 52, 281	F	65	BF	+	3	D	
5. Jacobi . .	New York Med. Jour., 1882, 36, 304	M	66	+	+	BPF	+	1	D	
6. Lockhart .	Montreal Med. Jour., 1891, 20, 1	F	28	+	+	PA	+	3		Surgical dilatation of the vagina.
7. Warren . .	Boston Med. and Surg. Jour., 1896, 134, 641	F	38	BPA	+	2	L	
8. Norris . .	Am. Med., 1906, 11, 478	F	32	..	+	BP	+	3	L	
9. Esau . . .	Folia Urol., 1907-1918, 1, 582	M	63	+	+	BPFA	+	..	L	
10. Prigl . .	Ztschr. f. Urol., 1909, 3, 163	F	43	0	..	BPFA bac.	+	3	L	
11. Warren Museum*	Quoted from O'Neil	M	35	BPF	+	1	D	Postoperative cystitis. Old tuberculo- sis of kidney and bladder. Suprapubic operation. Postoperative pyelonephritis. Enlarged prostate.
12. Legueu . .	Jour d'urol., 1917-1918, 7, 105	M	21	+	+	BPF bac.	+	3	L	
13. Wolferth and Miller	Appendix, this report 4425 (No. 13)	M	48	BF	..	3	D	
14. Wolferth and Miller	This report, Case I	F	55	+	+	BPFA	+	2	D	

* Specimen No. 4968, Harvard Medical School.

TABLE V.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN MEN WITH STRICTURES OF THE URETHRA.

Author.	Reference.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Bosc . . .	Bull. Soc. anat. de Par., 1827, 2, 84	72	+	+	FA	+	1	D	Catheterization attempted, but failed.
2. Hall . . .	Proc. Phila. Path. Soc., 1860, 1, 6	36	+	..	FBA	D	
3. Schrady . .	New York Med. Record, 1884, 25, 79	45	+	..	FA	+	..	L	Perineal section performed. Diabetes.
4. Tronchet . .	Quoted from O'Neill.	75	+	..	FA	+	2	D	
5. St. George Hospital*	Quoted from Pepin	+	2	D	Also enlarged prostate. Kidney abscesses.
6. Lennander and Lundberg	Quoted from Pepin, Upsala Läkaref. Förh., 1897, 3, 563	53	+	..	BPA bac.	+	3	D	
7. Nogues (Economos)	Jour. d'urol., 1922, 13, 37	54	+	..	BPF bac.	+	3	D	

* Specimen, Series 39, Subseries S.

TABLE VI.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN PATIENTS WHO HAD A STONE IN THE BLADDER.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Dolbeau . .	Traité Pratique de la Pierre dans la Vessie, 1764, p. 314 (quoted from Pepin)	M	26	+	+	PA	+	3	L	Cystotomy.
2. Dolbeau . .	Traité Pratique de la Pierre dans la Vessie, 1764, p. 314 (quoted from Pepin)	M	14	+	2	L	Cystotomy.
3. Deschamps .	Traité de la Taille, 1796 (quoted from Pepin)	M	FP	+	..	L	Cystotomy.
4. Stein . . .	Jour. Cutan. and Genito-urin. Dis., 1894, 12, 273	M	26	+	+	BPFA	+	2	D	Cystotomy.
5. Dean . . .	Practitioner, 1904, 72, 907	M	18	+	+	P	+	..	L	Stone in urethra; cystotomy.
6. Praeger . .	München. med. Wehnschr., 1906, 53, 1275	F	38	+	..	BPF	+	1	..	Pregnancy; abortion.

TABLE VII.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER DEVELOPING AFTER THE INJECTION INTO THE BLADDER OF IRRITANTS.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Substance injected.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Begouin .	Arch. clin. de Bordeaux, 1892, 1, 479	F	20	0	..	Sodium chloride	B	+	3	L	
2. Robinson	Albany Med. Ann., 1907, 28, 175	F	40	Hot normal salt solution, boric acid and vinegar	..	+	1	L	Necrosis due to irrigation or cystitis?
3. Mock . .	Ann. d. mal. de'org. génito-urin., Paris, 1911, 2, 1633	F	25	+	+	Ammonia solution	BPFA	+	3	L	Also pyelitis.
4. Mock . .	Ann. d. mal. de'org. génito-urin., Paris, 1911, 2, 1633	F	19	Sodium chloride and vinegar	..	+	3	L	Residual cystitis and pyelonephritis.
5. Morson .	Brit. Med. Jour., 1919, 1, 129	M	27	0	..	Potassium permanganate	B	..	3	D	Also gangrene of lungs.
6. Dawson .	Bull. Johns Hopkins Hosp., 1919, 9, 155	M	23	0	..	Potassium permanganate	No P No B	+	1	L	Only epithelium exfoliated.

TABLE VIII.—CASES OF NECROSIS OR GANGRENE OF THE BLADDER OCCURRING IN THE COURSE OF GENERAL INFECTIONS.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Infection.	Character of urine.	Exfoliation.	Depth of lesion.	Results.	Remarks.
1. Cossy . .	Arch. gén. de méd., 1843, 3, 24	F	18	0	..	Typhoid	D	Gangrene in patches.
2. Cossy . .	Arch. gén. de méd., 1843, 3, 24	F	..	+	+	Typhoid	BFA	+	1	D	
3. Cossy . .	Arch. gén. de méd., 1843, 3, 24	F	21	+	+	Typhoid	F	D	
4. Lemaire .	Bull. Soc. anat. de Paris, 1863, 38, 416	F	..	+	+	Typhoid	F	+	2	D	
5. Perriol . .	Le Dauphine méd., 1912, 36, 49	F	25	+	..	Typhoid	BPF	+	3	L	
6. MacGowan	California State Jour. Med., 1918, 16, 21	F	Pneumonia	BPFA	+	..	L	Pyelonephritis. Pyelonephritis.
7. Miller and Wolfert	Jour. Am. Med. Assn., 1922, 79, 1756	F	38	+	+	Typhoid	BPFA	+	2	D	
8. Miller and Wolfert	Jour. Am. Med. Assn., 1922, 79, 1756	F	30	+	+	Typhoid	BPFA	+	1	D	
9. Wolfert and Miller	Appendix, this report 2502 (No. 9)	M	71	Pneumonia	BF	..	1	D	
10. Wolfert and Miller	Appendix, this report 4160 (No. 10)	F	Broncho-pneumonia	1	D	
11. Wolfert and Miller	Appendix, this report 6430 (No. 11)	M	Pneumonia; tuberculosis of lungs	3	D	Diabetes and cardiac failure.
12. Wolfert and Miller	Appendix, this report 6702 (No. 12)	M	Acute malignant endocarditis	2	D	
13. Wolfert and Miller	Case IV, this report	F	72	0	0	Broncho-pneumonia	..	0	3	D	

TABLE IX.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER OCCURRING IN PATIENTS WITH LESIONS OF THE CENTRAL NERVOUS SYSTEM.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Central nerve lesion.	Character of urine.	Exfoliation.	Depth of lesion.	Result.
1. Wilks . .	Trans. Path. Soc., London, 1863, 15, 136	M	32	+	+	Acute paraplegia	..	+	2	D
2. Southam .	Med. Chron., Manchester, 1892, 17, 230	M	28	+	+	Dislocated seventh cervical vertebra	BPFA	..	2	D
3. Cathelin .	Chir. urin. de Guerre, 1919, p. 88	M	21	+	+	Bulbar injury	F	+	1	D
4. Cathelin .	Chir. Urin. de Guerre, 1919, p. 88	M	29	+	+	Injury of fifth and sixth dorsal vertebrae	F	+	1	L
5. Esau . .	Ztschr. f. urol. Chir., 1921, 8, 63	M	31	+	+	Wound of cord	BA	+	2	D
6. Wolfert and Miller	Appendix, this report 2469 (No. 1)	F	48	Hemiplegia tuberculosis; interstitial nephritis	B	..	1	D
7. Wolfert and Miller	Appendix, this report 3103 (No. 2)	F	Compression myelitis	1	D
8. Wolfert and Miller	Appendix, this report 3103 (No. 2)	M	Myelomeningitis	1	D
9. Wolfert .	Appendix, this report 6208 (No. 4)	M	Cerebrospinal	B	..	1	D
10. Wolfert and Miller	Case II, this report	M	67	+	+	Carcinoma of vertebrae and spinal cord	BAP	..	2	D
11. Wolfert and Miller	Case III, this report	F	47	+	+	Vertebra neoplasm with pressure on cord	P	..	3	D

TABLE X.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH TRAUMA SEEMED TO BE OF ETIOLOGICAL SIGNIFICANCE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Trauma.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Liston*	Quoted from Pepin	M	70	+	..	Fall from scaffold	..	+	..	D	Cystotomy.
2. Pepin	Thésis, Paris, 1893	M	57	+	+	Rupture of urethra	BPF	+	3	D	Several perforations of bladder.
3. Fenwick	Brit. Med. Jour., 1910, 1, 798	M	39	+	+	Fracture of pelvis	BPF	..	4	D	Complete destruction of bladder wall.
4. Perriol	Le Dauphine méd., 1912, 36, 49	F	23	Fracture of pelvis with perforation of bladder	BF	+	3	L	

* Surgeons' Museum, London, Specimen No. 1933.

Miscellaneous.

TABLE XI.—CASES OF NECROSIS OR GANGRENE OF THE URINARY BLADDER IN WHICH MISCELLANEOUS PREDISPOSING CAUSES WERE OPERATIVE.

Author.	Reference.	Sex.	Age.	Retention.	Catheterized.	Character of urine.	Exfoliation.	Depth of lesion.	Result.	Remarks.
1. Rouhault	Quoted from Pepin, Hist. de l'Acad. des sci. anat., 1714	M	..	+	+	..	+	2		
2. Tulpus	Observ. medicae, Lugduni Batavorum, 1716	F	B	+	1	L	
3. Boucher	Bull. Soc. anat. de Paris, 1841, 16, 139	M	..	+	+	D	Bilateral inguinal herniae.
4. Lee	Trans. Path. Soc. London, 1863, 15, 136	M	38	+	+	B	+	3	D	Abscess of scrotum.
5. Murchison	Trans. Path. Soc. London, 1868, 19, 281	M	42	0	0	BF	+	1	D	Stone (?).
6. Schwarz	Centrbl. f. Gynäk., 1880, 4, 121	D	Perforation of the bladder.
7. Orłowski	Centrbl. f. Chir., 1888, 15, 855	F	3	+	+	BPF	+	1	L	Dysentery.
8. Clarke	Trans. Path. Soc. London, 1888, 39, 164	M	36	+	+	BPFA	+	4	D	Perineal section; death from sepsis.
9. Falkenberg	Quoted from O'Neil, 1890	M	..	+	..	PF	+	..	L	Extravasation of urine.
10. Fenwick	Med. Soc. Trans., 1894, 17, 346	M	52	+	3	L	Difficulty in urination twenty-five years.
11. Kelly	Operative Gynecology, 1898, p. 351	F	..	+	+	1	L	Followed ovariectomy; died a year later.
12. Legueu	Bull. Soc. anat. de Paris, 1898, 73, 440	F	40	+	+	BPF	+	3	L	
13. Margulies	Quoted from O'Neil, Khirurgia, Moscow, 1904, 15, 158	+	+	BFP	+	3	L	Etiology obscure.
14. Prigl	Ztschr. f. Urol., 1909, 3, 163	M	54	+	+	BFA	..	1	D	Inserted pebbles in urethra.
15. Wolferth and Miller	Appendix, this report (No. 8)	F	35	1	D	Carcinoma of uterus secondary involvement of bladder.
16. Wolferth and Miller	Appendix, this report (No. 5)	M	14	1	D	Appendicitis; peritonitis; fecal and vesical fistulae.
17. Wolferth and Miller	Appendix, this report (No. 6)	M	1	D	Uremia; pyelonephritis right; hydro-nephrosis left.
18. Wolferth and Miller	Appendix, this report (No. 7)	M	69	R	..	3	D	Chronic interstitial nephritis.
19. Wolferth and Miller	Appendix, this report (No. 14)	F	1	D	Carcinoma of the vagina; bladder not involved.
20. Wolferth and Miller	Case V, this report	F	43	0	0	P	0	1	L	Cardiorenal disease.

TABLE XII.—AGES BY DECADES IN THE 105 CASES IN WHICH IT WAS RECORDED. YOUNGEST, THREE YEARS; OLDEST, SEVENTY-FIVE YEARS.

Age.	Total cases.		Cases without pregnancy.	
	Number.	Per cent.	Number.	Per cent.
1 to 10 years	1	0.9	1	1.6
11 to 20 "	10	9.5	7	10.9
21 to 30 "	33	31.4	17	26.6
31 to 40 "	38	36.2	17	26.5
41 to 50 "	10	9.6	9	14.1
51 to 60 "	4	3.8	4	6.2
61 to 70 "	5	4.8	5	7.9
71 to 80 "	4	3.8	4	6.2
Total	105	100.0	64	100.0

TABLE XIII.—SUMMARY OF DATA ON 153 CASES OF NECROSIS OR GANGRENE OF URINARY BLADDER.

Clinical conditions with which associated.	Number.	Male.	Female.	Retention.	No retention.	Catheterized.	Not catheterized.	Urine.				Exfoliation.	Depth of lesion.				Result.	
								Bloody.	Purulent.	Fetid.	Alkaline.		1.	2.	3.	4.	Died.	Lived.
1. Retropregnant uteri . . .	40	0	40	40	0	11	2	22	13	21	13	32	10	5	6	10	25	14
2. Labor	21	0	21	15	6	14	1	13	7	9	7	20	6	5	5	1	5	16
3. External pressure	11	0	11	6	3	6	2	8	7	5	4	7	0	4	4	1	4	7
4. Cystitis	14	7	7	7	1	7	0	10	11	9	6	13	3	3	7	0	6	7
5. Stricture of urethra	7	7	0	6	1	1	0	3	2	5	5	6	1	2	2	0	6	1
6. Stone in bladder	6	5	1	4	0	3	0	2	5	3	2	6	1	2	1	0	1	4
7. Irritants	6	2	4	1	3	1	0	3	1	1	1	4	2	0	4	0	1	5
8. General infections	13	3	10	6	2	5	0	6	4	8	4	6	4	3	3	0	11	2
9. Gen. nerv. sys. lesion	11	8	3	7	0	7	0	5	3	3	3	4	6	4	0	0	10	1
10. Trauma	4	3	1	3	0	2	0	3	2	3	0	3	0	0	2	1	3	1
11. Miscellaneous	20	11	7	10	2	8	2	9	6	7	2	11	10	1	5	1	12	7
Total	153	46	105	105	11	63	7	84	61	74	47	112	43	29	39	14	84	65

Thus it will be seen that various etiological factors may be considered as operative in these groups of cases, but that no one stands out obviously as a possible cause for all. Retention had not occurred in all cases and it is impossible to assert that it was not secondary in many of those in which it did occur. Pressure from the outside on the neck of the bladder was present in only a minority of the cases. There is no evidence that irritants were injected into the bladder in any but the 6 cases of Table VII. It may be argued that the ammoniacal decomposition of retained urine was a sufficient irritant cause in many others, but the absence of retention in some of the cases would seem to eliminate this possibility. Though certain definite nerve lesions occurred only rarely, Cathelin¹² felt that all the cases could be explained on some

nervous influence, even a lethargic mental state, such as occurs in typhoid, being sufficient; but he surely was not familiar with the reports of cases in pregnant women, in men with prostatic hypertrophy and in those with local infections.

Infection seems to us to demand most serious consideration since this might have occurred in all the cases, either by introduction with a catheter, by operation or by blood stream. But it is impossible to prove that this always occurred, and on pathological grounds infection does not seem essential to the production of a simple necrosis of tissue. Such necrosis occurs not infrequently in other portions of the body from a mere interference with blood supply, as in an extremity. That a non-infectious necrosis of bladder tissue theoretically may occur cannot therefore be denied. That infection does occur in many of the cases, however, seems equally evident. Whether or not there are any specific organisms that especially lead to this condition cannot be asserted until many more studies have been made.

We are therefore inclined to believe, on the one hand, with Haultain,¹ both on experimental and clinical grounds, that mere interference with the local blood supply is a sufficient cause in some instances, especially when only necrosis occurs, and, on the other, with O'Neil,² that infection may explain some. In addition there is a small group of cases due primarily to the direct effect of chemical irritants injected into the bladder. The other assigned causes are probably operative in only a predisposing way, retention and pelvic masses acting only insofar as they obstruct the circulation, enlarged prostates and strictures leading to retention, and often to infection, and central nervous system lesions interfering with bladder evacuation and so producing venous stasis.

Thus we have been led to the conclusion that there are three primary factors which may produce bladder necrosis: Infection, circulatory stasis and chemical irritants, and that these may be operative either singly or combined. When necrosis goes on to gangrene infection is probably always present.

Under this heading a few words may be devoted to the age incidence. Table XII indicates that 67.6 per cent occurred in the third and fourth decades. It might be thought that this was due to the large number of cases in women incident to pregnancy, but excluding these it will be noted that still the majority of the cases (53.1 per cent) fall into this period of life. No period of life is immune, however, 1 case occurring in a child aged three years and 1 in a man aged seventy-five years.

Morbid Anatomy. *Gross Appearances.* In conditions having such diverse predisposing factors as the necrotic and gangrenous affections of the bladder, it is to be expected that great differences in morbid anatomy will be found. The appearances of the lesions

vary according to the duration, extent and severity of the involvement and the presence or absence of exfoliation.

The situation of the destructive process is practically always on the inner side of the bladder wall. Necrotic muscularis and serosa surrounding healthy mucosa and submucosa have not been described. If the outer coats are affected the inner coats are also affected, and in the latter the necrotic process is usually found in the more advanced stage. We have attempted to tabulate from the reports in the literature and our own material the depths

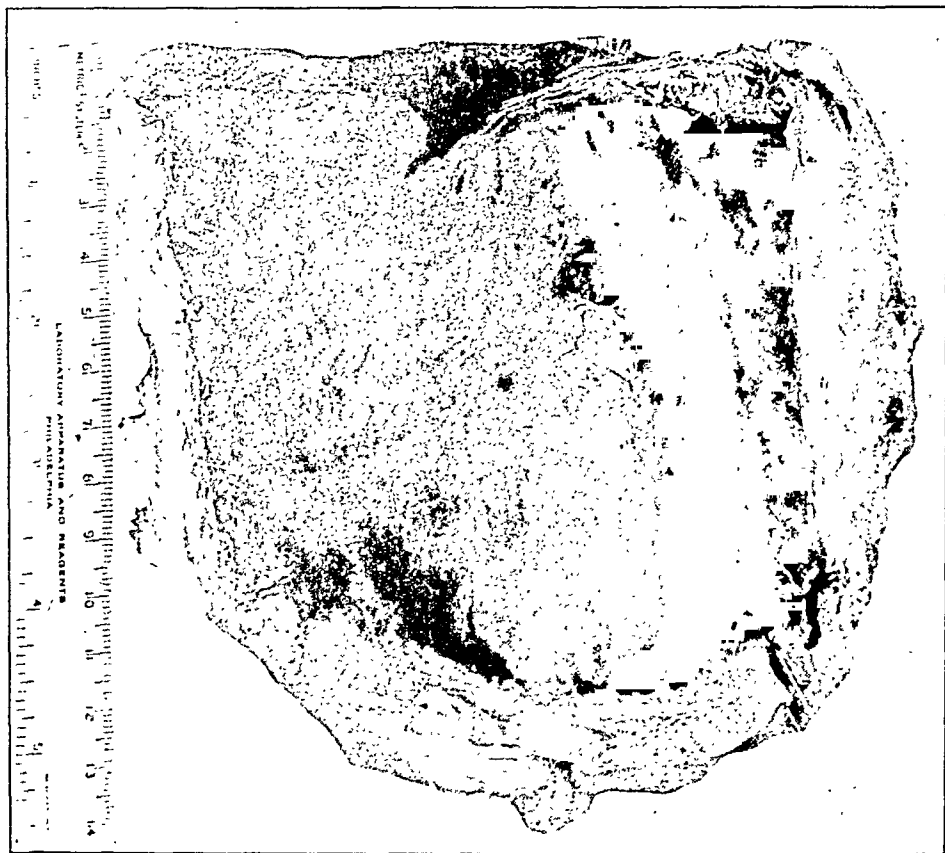


FIG. 1.—Photograph of interior of bladder showing widespread gangrenous involvement, which in places extended entirely through the greatly-thickened wall. There are present areas from which exfoliation has occurred. (Accession No. 141, Pathological Museum of the Philadelphia General Hospital. Courtesy of Dr. E. B. Krumbhaar.)

of the lesions. There are doubtless a number of faulty observations, but the figures may give some relative idea of the degree of bladder-wall involvement. In 43 cases the mucosa alone was said to have been affected; in 29 the submucosa also; in 39 the mucosa, submucosa and at least part of the muscularis; in 14 the entire thickness of the bladder wall was destroyed, either in a limited area or completely. Of the cases we report, in which microscopical

studies were made, the numbers in each group were 4, 5, 6 and 1, respectively.

The bladder is usually described as showing extensive necrosis or gangrene, but there are cases in which the extent of involvement is slight. One type is seen in the case reported by Dawson,¹⁸ in which, after the injection of an irritant, large sheets of epithelium were exfoliated, and indeed in many the entire inner wall was affected. Another type is that seen in our Case IV and Case V, in which localized areas of bladder necrosis were found in patients who had died of apparently unrelated conditions. This type, we believe, as a result of examining a number of bladders and discussing the question with pathologists who have had large experience in necropsy work, is not so very uncommon as a terminal event. It probably has little pathological or clinical significance, except as evidence of terminal failure in the nutrition of bladder tissue.

In the cases with grave lesions, which group includes the great majority tabulated, the area of involvement is usually widespread. In the early stages the mucosa is greatly swollen and hyperemic, and may bleed so freely that it is difficult to clear the bladder for cystoscopical examination. Whitish patches of pseudomembrane may be present. The color of the mucosa quickly changes to dirty gray, greenish or black. The necrotic inner portion of the bladder in some cases is seen to be separated in places with rolling up of the edges. Finally exfoliation occurs and the surface of the bladder then assumes a rough shaggy appearance. Incrustation with urinary salts is sometimes seen. The bladder wall is usually greatly thickened, even after exfoliation.

Exfoliation of the necrotic tissue was observed in 112 of the 153 cases reviewed and probably would have occurred in all, had the patients lived long enough. The slough separated as small fragments, large sheets or as an entire cast of the bladder. Most common is the separation of one large mass and a number of small fragments. In females large fragments frequently have been passed *per urethram*, and in at least three instances this has occurred also in males. In several cases fragments have been removed or expelled through a cystotomy incision. Sometimes they have been found floating in the bladder at autopsy. They are extremely foul-smelling, dirty white, gray or greenish in color, friable, and often gritty due to deposits of urinary salts. Portions of bladder tissue may sometimes be recognized on microscopical examination, particularly muscle fiber, but in many cases the material is so decomposed that nothing can be recognized.

After the acute process in the bladder subsides repair may take place to an extraordinary degree. According to O'Neil,² if the peritoneum is exfoliated the surrounding organs take part in the repair and a secondary sac is formed by inflammatory adhesions,

which later become changed into fibrous tissue. In cases with exfoliation of almost the entire bladder such sacs have been formed. Where the exfoliation has been more superficial the bladder becomes covered over with tissue that on cystoscopic examination may be indistinguishable from normal mucosa. The bladder sometimes recovers its normal capacity, but in the cases with more severe involvement it is liable to remain greatly contracted and to become distorted in shape.

Microscopical Appearances. The characteristic finding on microscopical examination is a necrosis of the bladder tissues. The various coats involved may still be recognizable, or the process may have extended beyond this stage. There is usually a marked cellular infiltration, often with many red cells and fibrin in the necrotic area and in the zone separating it from healthy tissue. Bacteria in great numbers can usually be found. Not infrequently areas of pseudomembrane with a network of fibrin, white and red cells and bacteria are found over the surface of the bladder.

In the less acute cases the cellular infiltration may be principally of the round-cell type and beginning connective-tissue proliferation in the zone of demarcation may be seen. This was observed several times in the cases reported in the appendix.

Clinical Features. Diagnosis. Necrotic and even gangrenous lesions of the bladder arising during the course of profound illness may escape the notice of the attending physician. Of the 14 cases collected in the appendix, all of which were under observation in a hospital, the diagnosis was not arrived at in a single instance, and in but 5 was a diagnosis of any bladder lesion made. A patient in an obtunded state may have no bladder symptoms, or, if he does, may be unable to call attention to them. Under such circumstances, unless marked urinary retention occurs, no special interest is likely to be devoted to the bladder. Retention is usually a precursor of necrosis or gangrene, but may not develop until later in the course of the disease, few cases failing to show it at some stage. Even in the absence of retention, however, if the urine is examined or inspected frequently no cases except those with the mildest and most limited areas of beginning necrosis will fail to give unmistakable evidence of severe disease along the urinary tract.

The urinary findings, therefore, constitute a very important diagnostic feature. As the condition begins to develop, an excess of leukocytes or perhaps a slight hematuria is found. The urine later becomes fetid, in some instances the odor being almost unbearable. It is nearly always alkaline in reaction and usually contains varying amounts of blood, pus, debris and many bacteria. The presence of macroscopical amounts of blood in the urine and the fetor, both of which often occur early, should lead immediately to the suspicion of bladder gangrene. Fragments of gangrenous bladder tissue or mucopus may be present.

Other suggestive signs are interruption of the stream of urine during catheterization and inability to empty a full bladder by catheterization. The latter in some cases has been due to the fact that complete exfoliation of the mucosa had occurred and the exfoliated sac was filled with urine. Interruption of the flow of urine is usually due to the plugging of the catheter by exfoliated membrane or mucopus.

In a number of the more recent cases the diagnosis has been made or confirmed by cystoscopic examination. When available this is not only the most satisfactory method of determining the diagnosis, but also of discovering the extent of damage to the bladder.

If any of the exfoliated tissue is expelled or evacuated by catheter and, by microscopical examination, some element of bladder tissue is recognized the diagnosis is confirmed beyond question. In some instances, however, the extruded substance is so decomposed that no recognizable structure can be made out.

In the differential diagnosis the principal conditions to be considered are simple cystitis, pseudomembranous cystitis and tumors of the bladder. The presence of some affection graver than one of the ordinary forms of cystitis will rarely be suspected unless attention is drawn to such urinary characteristics as those described above. These should lead to careful search in the urine for exfoliated material, not merely exfoliated bladder epithelium, such as sometimes occurs in ordinary cystitis but fragments containing underlying bladder tissue. Since these are usually not found until late in the course of the disease cystoscopy must be relied upon for early diagnosis.

Much has been made of the distinction between pseudomembranous cystitis and necrosis or gangrene of the bladder, particularly in the French literature. Pseudomembrane formation occurs as a result of intense inflammation of the bladder and consists of deposits of exudate on the inner surface, made up principally of fibrin and cells. The pseudomembrane may exfoliate and in this respect resemble necrosis or gangrene. In a number of cases, in which only clinical findings were reported, the diagnosis of pseudomembranous cystitis was based solely on the fact that no bladder structure could be recognized in the exfoliated material. This does not constitute a valid basis for differentiation. As has been pointed out, in some cases with true bladder exfoliation the tissue is so disintegrated that no bladder structure can be recognized. Moreover, pseudomembrane may cover over necrotic bladder tissue or some parts of the bladder may be gangrenous and others covered over by pseudomembrane (as in Case I). It seems more in accord with the actual facts observed, therefore, to regard pseudomembranous cystitis not as a clinical entity to be differentiated from other forms of bladder disease, but rather as a form of inflammatory

reaction, which may occur during the course of intense cystitis and also in necrotic or gangrenous conditions.

Exceptionally a mistaken diagnosis of tumor of the bladder is made either on account of the urinary findings or the fact that bimanual examination discloses marked thickening of the wall. The clinical diagnosis of cancer was made in 2 of the cases reported in the appendix, and in 1 of these, after gross anatomical examination, the diagnosis was still adhered to, microscopical study being required to demonstrate its incorrectness. Also in Cases I and II this clinical diagnosis was made even after cystoscopic examination.

Usually there should be no difficulty in differentiating the two types of conditions, but occasionally there will be. In the absence of obvious predisposing factors to explain the onset of necrosis or gangrene, the possibility of underlying neoplasm naturally presents itself, and in some cases one may not be able to exclude malignancy by any of the methods of clinical study. Case I illustrates this point. The presence of gangrene of the bladder wall was clearly recognized on cystoscopy by Dr. Keene, but the thickness and induration of the bladder revealed by bimanual examination made him suspect the presence of cancer.

Complications. Gangrene of the bladder may be accompanied by general sepsis, but even cases with severe local disease may have no elevation of temperature or marked constitutional disturbance. Nephritis and uremia have occasionally been described as complications. Perforation of the bladder wall sometimes occurs and when it does the infected urine may escape into the general peritoneal cavity and set up a virulent peritonitis. The peritoneum is sometimes protected, however, by the formation of pericystic adhesions, even in cases where practically the entire bladder is exfoliated. In a few cases following perforation of the bladder extravasation of urine occurred about the genitalia, with the usual serious result of this condition. Infection of a kidney, such as pyelonephritis or pyonephrosis, was described in only 6 cases collected from the literature. We judge these complications to be far more frequent than is indicated by that figure as it was observed in 5 of the cases we report.

Prognosis. Of the 153 cases we have collected 65 lived, 84 died and in 4 the outcome was not stated. It would be fallacious, however, to estimate the mortality from these figures. A number of the cases (including those in the appendix) were collected from pathological material. It is unquestionable, furthermore, that many cases, particularly the milder ones, are overlooked entirely or regarded merely as simple cystitis. The mortality is greatly influenced by the type of morbid process which predisposes to the bladder lesion. Thus we find a very high mortality in those cases developing as a result of general infections, diseases of the central

nervous system and retrodisplaced pregnant uteri lodged in the pelvis. On the other hand, the mortality is comparatively low in cases developing during or after child-birth. The mortality is much higher in men than in women. Among 45 men, 12 lived and 33 died, while among 102 women, 52 lived and 50 died. This difference in mortality between the sexes is doubtless due largely to the easier drainage of the bladder through the urethra in women.

In the patients who lived, variable results as to recovery of bladder function were observed. In some there was complete or almost complete recovery. In the severe cases, however, there was usually definite limitation of bladder capacity and in several instances complete incontinence of urine.

Treatment. The fact that no cases of necrosis or gangrene of the bladder as complications of pregnancy and labor have been reported since 1893 (see Tables I and II) would seem to indicate that modern aseptic technic and the better general management of these conditions in modern times are important prophylactic measures. In general the avoidance of prolonged over-retention of urine, careful asepsis in catheterization, prevention of prolonged pressure against the bladder wall and promptness in the treatment of stone in the bladder, urethral stricture and enlarged prostate undoubtedly would lower the incidence of necrosis or gangrene. Rarely, in cases of severe general infection and in lesions of the central nervous system they appear to be unavoidable.

Very little is to be found in the literature concerning the actual management of these grave bladder lesions. In the vast majority of cases conservative methods of local treatment have been employed, such as frequent catheterization or constant drainage to avoid over-distention and irrigation of the bladder with normal salt solution, boric-acid solution or strong germicidal agents.

Haultain¹ stated that there could be little doubt that the result inevitably would be fatal in males unless the exfoliated sac were removed artificially. Later reports have shown, however, that exceptionally recovery has ensued after spontaneous expulsion of the slough *per urethram*. O'Neil² has affirmed that the results of operation in males have been excellent, but that the mortality is extremely high in non-operated cases. Analysis of the material now available substantiates O'Neil's statement. Cystotomy had been performed in 9 of the 12 males who recovered, and in only a few (3, possibly 1 or 2 more) of the 33 fatal cases. It should be pointed out, however, that in most cases the operation was done not on account of the bladder lesion alone, but because of the presence of some added factor, such as stone, urethral stricture or enlarged prostate. Thus the good results were doubtless contributed to by the removal of the causes of the bladder affections. Nevertheless, the present state of our knowledge would seem to warrant the statement that cystotomy should be undertaken in all

male patients in whom extensive necrotic or gangrenous bladder lesions have been discovered and in whom the general condition would justify such a procedure.

In females a more conservative position may be assumed with respect to operation on account of the fact that drainage through the short and dilatable urethra is much better than in males, and sloughs, even enormous ones, frequently have been expelled. It seems reasonable to suppose, however, that some of these cases whose progress was not satisfactory might have been benefited, although there is no satisfactory data to establish the fact, had cystotomy been done and better drainage secured. We believe that cystotomy should be given a trial under such circumstances.

Summary. 1. One hundred and fifty-three cases of necrosis or gangrene of the urinary bladder are reviewed, 21 of these (including 2 recently reported by us) being new ones.

2. It is suggested that the affection is not so rare as the scarcity of reports in the literature would indicate.

3. No single etiological factor can be determined at this time for all the cases, but either infection, circulatory disturbance or chemical irritants, or a combination of these factors, would seem to explain the causation in practically all instances.

4. The pathology and clinical features are reviewed.

5. It is suggested that cystotomy might be a justifiable and beneficial procedure in the more severe cases.

APPENDIX.

(Abstracts of autopsy records of 14 cases exhibiting either necrosis or gangrene of the urinary bladder which were discovered in a review of 5250 autopsy protocols in the Pathological Laboratory of the University of Pennsylvania.—Courtesy of Dr. Allen J. Smith.)

1. *Autopsy No. 2469.*—R. J., female, colored, aged forty-eight years; patient of Dr. Spiller at Philadelphia General Hospital. *Clinical diagnoses:* Hemiplegia; tuberculosis of the lungs and intestines; interstitial nephritis. *Gross findings* at autopsy (March 25, 1909): Extensive tuberculosis of the lungs, intestines and lymph glands; chronic abscess of the kidney (probably tuberculosis); pyelonephritis; amyloid infiltration of the spleen; gangrenous cystitis, the mucosa at the fundus being green-black and ulcerated. The contents of the bladder were cloudy and red. No *microscopical* report on bladder.

2. *Autopsy No. 3103.*—C. M., female, white, aged fifty years; service of Dr. Spiller at Philadelphia General Hospital. *Clinical diagnosis:* Compression myelitis, myocarditis and nephritis. *Gross findings* at autopsy (March 14, 1909): Bladder filled with greenish, purulent and granular material; bladder wall thickened;

mucosa of bladder greenish and shows distinct proliferation with dark and necrotic surface. *Microscopical report*: Muscle bundles fairly compact; submucosa the seat of connective-tissue overgrowth and small round-cell infiltration in circumscribed areas, over which the mucosa has disappeared; some free blood present on surface.

3. *Autopsy No. 4171*.—E. H., male, white, aged fifty-two years; patient at Philadelphia General Hospital. *Clinical diagnosis*: Myelomeningitis. *Gross findings* at autopsy (April 25, 1913): Urine purulent; inner bladder wall thick, edematous and black. *Microscopical findings*: Mucosa entirely missing, muscle bundles large and an increase of connective tissue in the muscular layer.

4. *Autopsy No. 6208*.—H. S., male; patient of Dr. Myers, Philadelphia General Hospital. *Clinical diagnosis*: Cerebrospinal disease and ulcerative cystitis. *Gross findings* at autopsy (September 12, 1919): Right pyonephritis; brownish, bloody fluid in the bladder; wall of bladder overlaid with necrotic grayish-yellow membrane; when membrane was scraped off a slaty color remained (diagnosed acute necrotic cystitis). *Microscopical findings*: Entire bladder wall edematous; mucosa entirely replaced by a process of necrosis, with infiltration of small round and polymorphonuclear cells, this process involving the deeper layers as well. Over the necrotic mucosa was a fibrinous exudate.

5. *Autopsy No. 857*.—F. S., male, aged fourteen years; patient of Dr. Edward Martin at University Hospital. *Clinical diagnoses*: Appendicitis, peritonitis, fecal fistula, secondary vesical fistula. *Gross findings* at autopsy (February 27, 1906): Bladder wall somewhat thickened; mucous membrane of the bladder was a mass of necrotic areas alternating with areas containing thick blackish-green diphtheritic membrane; there was an opening at the fundus into the inflammatory mass in left groin and so to fecal fistula. No *microscopical report* on the bladder tissue.

6. *Autopsy No. 1864*.—W. M., colored; patient at University Hospital. *Clinical diagnosis*: Uremia. *Gross findings* at autopsy (December 18, 1907): Gangrenous cystitis with areas of black discoloration and calcareous deposits, urethritis; right pyelonephritis and left hydronephrosis. The bladder contained viscid deep-red fluid. The wall was much thickened, there being great profusion of rugæ over the mucous surface. The mucosa was deep red in color with spots of black. To palpation there was a distinct grittiness, suggesting mineral material. Urethral submucosa exposed in places. *Microscopical findings*: Loss of mucous membrane of the bladder, the inner surface of bladder being covered by mass of loose fibrous tissue containing leukocytes and plasma cells. Some calcification present.

7. *Autopsy No. 2458*.—W. P., male, white, aged sixty-nine years; patient of Dr. Christian at Philadelphia General Hospital. *Clinical diagnoses*: Epithelioma of the bladder and chronic interstitial

nephritis. *Gross diagnoses* at autopsy (March 22, 1909): Scirrhus carcinoma of the bladder, gangrenous cystitis and ascending pyelonephrosis. Bladder was dilated and contained dark-red, cloudy fluid. Numerous nodular areas were observed and these seemed to infiltrate the muscle and surrounding areas. The inner surface of bladder wall was gray and black in color. *Microscopical findings*: Mucosa and submucosa missing, muscular layer (inner part) necrotic. No signs of carcinoma.

8. *Autopsy No. 7341*.—P. F., female, aged thirty-five years. *Clinical diagnosis*: Carcinoma of uterus with secondary anemia. *Gross findings* at autopsy (September 12, 1921): Small ovarian cyst adherent to bladder; soft gangrenous mass in lower portion of uterus; bladder greatly thickened and inner surface covered with white material; carcinoma at inferior portion of bladder (specimen in Museum). *Microscopical findings*: Acute necrotic cystitis; carcinoma, primary in uterus.

9. *Autopsy No. 2502*.—W. P., male, white, aged seventy-one years; patient of Dr. William Hughes in Philadelphia General Hospital. *Clinical diagnosis*: Croupous pneumonia, cancer of the liver, chronic interstitial nephritis and myocarditis. *Gross diagnoses and findings* at autopsy (April 10, 1909): Croupous pneumonia, chronic interstitial nephritis, cirrhosis of the liver, obstruction of common bile duct and gangrenous cystitis. The bladder contained cloudy, red-black, foul-smelling urine. The mucosa was green-black and covered with opaque white material. No *microscopical report* on bladder tissue.

10. *Autopsy No. 4160*.—E. H., female, white, aged seventy-six years; patient at Philadelphia General Hospital. *Clinical diagnoses*: Myocarditis and carcinoma of the bladder. *Gross findings* at autopsy (April 18, 1913): Exudation over the inner bladder wall and black spots. *Microscopical findings*: Mucosa entirely missing, submucosa thickened, muscularis thickened and infiltrated with fibrous tissue and round cells. No evidence of carcinoma.

11. *Autopsy No. 6430*.—J. L., male; patient of Dr. Morgan at Philadelphia General Hospital. *Clinical diagnoses*: Chronic ulcerative pulmonary tuberculosis and miliary tuberculosis. *Gross findings* at autopsy (February 14, 1920): Diffuse and extensive ulceration of the bladder (possibly tuberculous). *Microscopical findings*: Mucosa replaced by a necrotic mass, this extending into the muscular layer. The muscle coats were edematous and some muscle fibers were swollen and broken with an increase of fibrous tissue between the bundles and exudation of leukocytes and lymphocytes. The serosa was fibrosed, edematous and ragged.

12. *Autopsy No. 6702*.—K., male. *Clinical diagnosis*: Old cardiac disease and acute malignant endocarditis. *Gross findings* at autopsy: Bladder showed patches of superficial ulceration overlaid by dirty yellow, adherent membrane with granular mineral

deposits. Thick turbid material covered the entire inner surface. *Microscopical findings:* Subepithelial parts showed hemorrhagic in some places, edematous in others and necrotic in still others. In certain areas mucosa was absent and the submucosa necrotic. The sloughing membrane consisted of highly disintegrated leukocytes, bacteria and necrotic tissue.

13. *Autopsy No. 4425.*—C. H., male, colored, aged forty-eight years; patient at Philadelphia General Hospital. *Clinical diagnoses:* Endocarditis, cystitis and enlarged prostate. *Gross findings at autopsy (March 2, 1914):* Chronic catarrhal cystitis with phosphatic incrustations; foul-smelling chocolate-brown urine; inner surface of bladder encrusted with gritty white material and irregular areas of brownish-red material. *Microscopical findings:* No mucosa or submucosa; superficial parts necrotic; muscular coats separated by broad bands of old fibrous tissue and masses of red blood cells; on mucosal side the muscularis extremely infiltrated by erythrocytes and muscular fibers were granular and the nuclei fragmented and shrunken. The most superficial parts were entirely necrotic.

14. *Autopsy No. 6621.*—M. U., female; patient of Dr. Joseph Sailor at Philadelphia General Hospital. *Clinical diagnoses:* Chronic myocarditis and cystitis. *Gross findings and diagnoses at autopsy (May 15, 1920):* Carcinoma of upper vagina; bladder not involved, but left ureter blocked by a firm nodule. The inner bladder wall was bright red with a few grayish dirty areas. *Microscopical findings:* No carcinoma of the bladder, but the mucosa was necrotic.

REFERENCES.

1. See Table I, No. 37.
2. See Table II, No. 19.
3. See Table VIII, No. 7.
4. See Table XI, No. 2.
5. Catarrh de la Vessie, Thésis, Paris, 1815.
6. Précis d'Anatomie Pathologique, 1829.
7. See Table IV, No. 1.
8. Ann. des mal. des Organes Genito-urinaires, 1887, 5, 385 and 445.
9. Pathologische Anatomie, Leipsic, 1921, Ed. 5, 2, 517.
10. See Table VIII, No. 1.
11. See Table VII, No. 3.
12. See Table IX, No. 3.
13. See Table X, No. 2.
14. See Table IV, No. 12.
15. See Table V, No. 7.
16. Quoted from O'Neill.
17. Die experimentelle Diphtherie, Leipsic, 1883.
18. See Table VII, No. 6.

MEDICAL BILIARY DRAINAGE.

By A. SACHS, M.D., M. C. HOWARD, M.D.,

AND

M. W. BARRY, M.A.,

OMAHA, NEB.

(From the Department of Medicine, Creighton University, Omaha, Neb.)

THE literature has contained many interesting articles on this timely subject during the past four years, and directly opposite views exist as to its real value. Some consider it a valuable diagnostic aid in differentiating lesions of the upper right quadrant, and also an excellent therapeutic adjunct in the treatment of biliary disease, while others claim that it has very little value, and question its reliability.

The extremist on any subject is usually wrong, as is also the pessimist. If any subject is to be brought before the medical profession forcibly, it usually requires an enthusiast to do so. This Lyon has accomplished, and he deserves credit not only for arousing new interest in biliary disease, but also in opening the way for new physiological and chemical investigations.

Since our last publication on biliary drainage, in May, 1921, we have continued our work, constantly striving to arrive at the truth in an unprejudiced and scientific manner, and it is with this end in view that we offer this publication. We have continued our conservative view-point and while not being able to agree with all facts, believe that it undoubtedly has some value as a diagnostic and therapeutic agent.

Some of the greatly disputed points are as follows:

1. Does the gall-bladder contract?
2. Does the gall-bladder empty by a definite reflex of sphincter relaxation and gall-bladder contraction?
3. Are there other factors which assist the gall-bladder in expelling part of its contents?
4. Is the gall-bladder a mere reservoir, or has it definite function?
5. Is "B" bile gall-bladder bile?
6. Is there a chemical change which can account for the dark or "B" bile, or in other words, an oxidation of pigments?
7. Is all dark colored bile "B" bile?
8. Does magnesium sulphate have specific action, or can other substances likewise cause sphincter relaxation?
9. Is medical biliary drainage of any aid diagnostically?
10. Is medical biliary drainage of any value as a therapeutic procedure?

11. In what manner is biliary drainage of value and would gastric lavage afford as much relief as biliary drainage?

It is not the purpose of this paper to give detailed anatomical and physiological descriptions of the organs under consideration, yet it is well to review just one or two points. The gall-bladder has a capacity of about 50 cc. Its walls consist of fibro-elastic tissue, and unstriped muscle fibers, which are longitudinal, circular and oblique. The common bile duct is guarded by a sphincter called the sphincter of Oddi. It is conceded by most men that this is a definite sphincter and has sphincteric action. It was first described by Oddi in 1887, confirmed by Hendrickson in 1898, also by many other observers since then.

It is by the tonus of this sphincter that the bile is reverted into the gall-bladder, and through its relaxation that the bile is permitted to flow into the duodenum. The flow of bile in a normal dog is intermittent, and occurs in spurts; however, on removal of the gall-bladder its flow becomes more continuous. There are certain species of animals that do not possess a gall-bladder, in which the flow of bile is continuous, namely the horse, the deer, the rat, and the pocket gopher. The sphincter of Oddi in this species is histologically the same as those with a gall-bladder.

Judd and Mann have found that in a normal anesthetized dog the sphincter of Oddi will resist about 150 mm. of water pressure before being relaxed. However, after the removal of the gall-bladder, the sphincter resistance was lowered and it required only 40 mm. of water pressure for its relaxation. In animals without a gall-bladder, the sphincter resistance is also low, being from 30 to 70 mm. of water, hence the continuous flow of bile in this species.

Johnson has demonstrated that the duration of sphincter relaxation varied according to the nervous state of an animal. He frightened dogs and bile ceased to flow, however, on the same dogs, while sleeping, a continuous flow for one hour and a quarter was noted. This observation can be corroborated in humans, for oftentimes during the first medical drainage no free drainage of bile is obtained, even though the tube is in its proper place and the duodenum is douched several times with magnesium sulphate. On the second and third drainages the patient's fear has vanished, and better drainages are obtained.

It is a well known fact that gastric chyme rich in fats, proteoses and peptones cause an excessive secretion of bile, because it is needed for their digestion. Carbohydrates on the other hand call forth very little secretion of bile, but a large amount of pancreatic secretion.

All patients do not have the same stature. Some have a wide epigastric angle, and others a narrow one. This immediately informs us that the relationship of liver, gall-bladder, bile ducts,

and duodenum, are not the same in all individuals, hence it must be borne in mind that some gall-bladders and cystic ducts are joined at a more acute angle than others. Graham in his experiments on dogs has demonstrated that position or gravity was a factor in expulsion of dye injected into the gall-bladder. This fact will be taken up more in detail at a later time.

The valves of Heister are not always arranged the same in cystic ducts. Occasionally an anomaly of these valves or folds act as an obstruction making it difficult to empty manually a gall-bladder, however, these same gall-bladders can be emptied more readily if they are pulled more or less taut. Barker believes these valves to be under sympathetic control and act to as a protection to the inflow of bile. They are unquestionably placed there for a definite purpose, hence it seems logical that they may at times act as a hindrance to the outflow as well as to the inflow of bile, which is a fact worth considering before diagnosing obstructions of the cystic duct.

The technic of passing the duodenal tube, preparation of the patient, etc., has been given in numerous publications, and need not be again repeated. However, it might not be amiss to state that we feel that laborious washing with permanganate, lavis, and other antiseptics are unnecessary, as has been demonstrated by our bacteriological studies, and confirmed by Smithies. Also, Escherich, Hess and McNeal and Chase all found that the normal fasting duodenum is usually free from organisms. Astringents themselves may be irritant, and occasionally produce a duodenitis. Careful and frequent lavaging will cleanse the stomach and duodenum in just as efficient a manner for all purposes, as the use of antiseptics and astringents.

One point which is brought out by Lyon and bears especial emphasis, is the slow feeding of the last 20 cm. of the duodenal tube, for it is in this last procedure that curling of the tube in the stomach so frequently occurs.

1. DOES THE GALL-BLADDER CONTRACT?

The gall-bladder possesses circular muscle fibers which were placed there for some purpose, and the most logical one is that they were necessary for gall-bladder contraction. In 1894 Doyon carefully studied the innervation of the gall-bladder and bile ducts. In 1905, just eleven years later, Bainbridge and Dale covered the same ground, and although they disagree as to the effect produced by splanchnic stimulation, both recorded gall-bladder contraction. From the elaborate experiments of Bainbridge and Dale, one can readily see the difficulties encountered in registering actual gall-bladder contraction. Contractions of the abdominal viscera, activity of adjacent contractile organs, changes in the volume of the liver, may also record rises in gall-bladder pressure, simulating gall-bladder contraction. However, by their careful technic, they

were able to overcome these difficulties. In one of their experiments with adrenalin, they visualized small waves of contraction.

Okada also recorded rhythmic contractions of the gall-bladder and found the contractions were increased after a meal of meat. W. A. Johnson noted a minute wave of contraction in the gall-bladders of two dogs operated under local anesthesia. The contractions were very small and were at no time of sufficient force to empty the gall-bladder, a point of great importance, and which will be discussed later.

Freese also recorded gall-bladder contractions and measured the contractile force, finding that the maximum force of its contraction did not materially exceed the maximum secretion pressure of bile.

Crohn, Reiss and Radin, in experiments on dogs, report that they were unable to note any gall-bladder contraction. They also report that the sphincter (Oddi) while capable of contractility and closure under mechanical or faradic stimulation, acted normally very little as a sphincter. The flow of bile was continuous, not interrupted or rhythmic, and no functional use of the sphincter muscle was observed. On strong faradic stimulation of peripheral end of the right vagus, they noted general abdominal contraction of intestines, diaphragm and stomach, and with these contractions, the expulsion of blue colored bile was observed, the gall-bladder having previously been injected with a methylene blue solution so as to recognize bladder bile.

Gall-bladder contractions are difficult to visualize, and if definitely recorded and seen by others, it is difficult to believe they do not exist. The maximal contractile force is only slightly over that of liver secretion pressure, hence, it is easy to understand why gall-bladder contractions may be overlooked.

Another favorite argument is that no surgeon has ever seen gall-bladder contraction. Some individuals have the erroneous idea that the gall-bladder forcibly contracts and immediately expels all of its contents. However, this does not take place, for only minute spurts of bile occur, and the gall-bladder never completely empties itself. When the gall-bladder is not distended, it is flaccid, and not in the state of contraction.

That gall-bladder contractions exist can hardly be questioned. However, the contraction force being so minimal, it is hard to believe that it alone can account for expulsion of gall-bladder contents, and in our opinion, it is only one of the factors which assist in this process.

2. DOES THE GALL-BLADDER EMPTY BY A DEFINITE REFLEX OF SPHINCTER RELAXATION AND GALL-BLADDER CONTRACTION?

Meltzer, in 1917, described the law of contrary innervation, and compared the gall-bladder with its sphincter to the urinary bladder and its sphincter. He cites the experiments of Rost,

who found that the injection of peptone and albuminoses through a duodenal fistula of a dog, was followed by an immediate discharge of bile, and he believed the same was produced by a reflex act causing a relaxation of the duct sphincter, and simultaneously a contraction of the gall-bladder. From the foregoing and other experiments, Meltzer believed that the gall-bladder and its sphincter were regulated by a definite reflex mechanism dominated by the law of contrary innervation.

Bainbridge and Dale saw no reflex contraction of the gall-bladder with relaxation of the sphincter, either by electrical stimulation or application of 0.4 per cent HCl. Their experiments were performed under anesthesia, and hence these authors state that this was no evidence as proof against the law of contrary innervation.

Okada found at times a distinct increased gall-bladder contraction by administration of 0.4 per cent HCl, and also with olive oil, not constant enough however, to draw definite conclusions.

A point in favor of Meltzer's law is an experiment by Judd and Mann previously reported in this paper, namely, that in a normal dog, the sphincter resistance is 100 to 150 mm. of water pressure. In dogs with the gall-bladder removed, the sphincter resistance drops to 40 mm. water pressure, and the ducts dilate. The only logical explanation of this lessened sphincter resistance and duct dilatation after removal of the gall-bladder must be through some disturbance produced by injury to the nervous mechanism controlling the relationship between the gall-bladder and duct sphincter. In animals without a gall-bladder, duct resistance is also lower than in those with a gall-bladder.

Harer, Hargus and van Meter believe this lessening of pressure by gall-bladder removal depends to a certain extent on the development of the muscle of the duct sphincter, because Rost found that after cholecystectomy, dogs may be divided into two groups; one group with well developed sphincter muscles continued to discharge bile into the duodenum intermittently until the common duct and ampulla became so widely dilated as to paralyze the muscle of Oddi. In other dogs, with poorly developed sphincter muscles, the bile was discharged continuously, and there was no dilatation of ducts. Sphincter development is important but cannot entirely explain the above, because Judd and Mann found a drop in sphincter resistance after gall-bladder removal, even though the duct sphincter was well developed, as evidenced by duct dilatation.

Clinically and experimentally, one may get sphincter relaxation without apparent expulsion of gall-bladder contents. Anyone having made use of medical biliary drainage has noted only one type of bile may be aspirated after repeated instillations of magnesium sulphate, even though the gall-bladder is intact and apparently normal. This cannot be used as an argument for or against the law of contrary innervation, because on one day a poor drainage

may occur and then several days later, in the same patient, all types of bile may be recovered.

Several men also report that in dogs in which the gall-bladder is injected with a dye so as to determine bladder bile, no dye was recovered after instillation of magnesium sulphate, HCl, peptone, etc.

In our experiments on decerebrated dogs we were able at times to recover spurts of dye by instillation of magnesium sulphate into the duodenum, and at times no dye was recovered. These experiments were not performed to prove or disprove the law of contrary innervation because no attention was paid to respiration, contraction of neighboring organs, etc. It is only mentioned here to show that no dye being recovered is no argument for or against the law of contrary innervation.

While it is logical to assume that the law of contrary innervation holds true as regards the gall-bladder and its sphincter, definite scientific proof is lacking, and more work is needed to prove this valuable hypothesis.

3. ARE THERE OTHER FACTORS WHICH ASSIST THE GALL-BLADDER IN EXPELLING PART OF ITS CONTENTS?

From the experiments of Freese and others as stated before, the contractile force is minimal and it seems doubtful if this factor alone can account for the expulsion of bile from the gall-bladder.

The experiments of Bainbridge and Dale definitely show that the contraction of the abdominal muscles and diaphragm, changes in the volume and turgescence of the liver, the activity of adjacent contractile viscera could all record increase in gall-bladder pressure, and hence in humans may be a factor in gall-bladder expulsion.

Johnson has definitely shown that the intermittent flow of bile bears a definite relation to respiration and that inspiration is undoubtedly a factor which aids gall-bladder expulsion. This can also be observed clinically; if, during a biliary drainage the bile flow commences to lessen, and then the patient is instructed to take several deep breaths, the flow is again resumed. Graham has verified Johnson's findings and demonstrated that position or gravity is also a factor in aiding the expulsion of injected dye from the gall-bladder of dogs. However, in human beings in the sitting or standing posture, the gall-bladder is usually lower than the cystic duct, and hence gravity cannot materially aid in its emptying process.

Harer *et al.* quote J. E. Sweet, who believes that the gall-bladder is emptied of its contents or part of its contents by pressure of the congested liver and the distended stomach during digestion, and by the milking action of the peristaltic waves as they pass down the duodenum. As the waves progress they act on the intramural portion of the common bile duct, just as the hand of the milkmaid acts on the teat in milking a cow. A slight negative pressure is

set up in the common duct and the bile flows into the duodenum. The valves of Heister are so constructed as to assist the entrance of bile into the gall-bladder, but once there, they make its withdrawal more difficult. Sweet therefore concludes that the only logical explanation of emptying the gall-bladder is by means of pressure from adjacent distended and congested organs, and by the milking action of the duodenal peristaltic waves.

Werelius believes that the gall-bladder has a suction bulb action similar to a stomach tube with its bulb.

The normal gall-bladder wall possesses a certain amount of elasticity or tone and when the sphincter is relaxed, this same elasticity or tone may also be a factor which aids the gall-bladder in emptying part of its contents. It is agreed by all that forceful contraction does not occur, and as we have reported in a previous article, it appears to be more of a collapse than a contraction.

Syphonage may be an added factor which aids the other expelling agents in medical biliary drainage. The sphincter being relaxed by HCl, peptone, magnesium sulphate, or other salts, and the bile flow started, it is logical to assume that syphonage may materially aid the other expelling forces.

From the various theories reported it seems most probable that no one factor is responsible for the gall-bladder expulsion, but rather a combination of several and perhaps the least important of all is gall-bladder contraction.

4. IS THE GALL-BLADDER A MERE RESERVOIR, OR HAS IT DEFINITE FUNCTION?

The function of the gall-bladder has long been a disputed question, and a diversity of opinion still exists as to its real function.

A cholecystectomy may be performed and the patient remains in apparent health for years. This has led many to believe that the gall-bladder has no essential function. This fact alone is not sufficient proof, inasmuch as Nature compensates for the loss of any organ, and this is likewise true with the gall-bladder, for when it is removed the ducts dilate, which is Nature's method toward compensation for its loss.

In animals that have no gall-bladder, the ducts are larger, which again may be Nature's method of compensating for the absence of a gall-bladder.

Rous and McMaster have experimentally proven that the gall-bladder has a definite concentrating function and is able to concentrate bile ten fold. They have also demonstrated that as long as the gall-bladder or part of the cystic duct was left, pigmented bile was present; however, if these structures were removed in their entirety, no pigmented bile was present and only the so-called white bile of surgeons was found. They likewise found that the gall-bladder secreted more mucus per surface area than any other organ, and also that it secreted considerably more mucus than the bile ducts.

The normal or static gall-bladder always contains darker pigmented bile than the liver or bile ducts. Fitz found that gall-bladder bile from cases having cholecystitis with stones, was less pigmented than those without stones. This is not a fast rule, for in some cases of cholecystitis with static bile and soft stones, dark pigmented bile is present. The concentration of bile can hardly explain this change, hence we must otherwise account for the oxidation of these pigments. It is claimed by some that an oxidase is present in the gall-bladder, hence an oxidation of bilirubin to biliverdin. Fitz reported that gall-bladder bile was acid and not alkaline, as has been generally accepted by most men. We have found in test-tube experiments that if alkalies are added to yellow ox bile, they remain yellow; if however, graded quantities of dilute hydrochloric acid was added, it became green more readily as the concentration of acid advanced. It was noted that specimens with a pH of 6.4 or less invariably became green on standing, while those with a pH higher than 6.4 remained yellow. (This point will again be discussed under "B" bile.) The acidity of bile undoubtedly aids in its oxidation. However, it does not fully explain all dark biles, and we are at present working on this problem.

It is supposed by some men that the mucus of the gall-bladder might be a factor in the oxidation of pigments. However, proof is still lacking. Some claim that it is merely a reservoir for the storage of bile. Others claim that it is a mere buffer in the circulation of bile, equalizes its pressure and protects the pancreas.

It seems logical that the gall-bladder may equalize pressure in the biliary system; however, that it is needed for protection of the pancreas does not seem probable, as demonstrated by recent work of F. C. Mann and Giordano on the bile as a factor in pancreatitis. In this article they state that the number of instances in which the anatomical arrangement, in the relationship of the common duct to the pancreatic duct, that would permit bile to pass into the pancreatic duct, is very small. They also found that the percentage of instances where mechanical obstruction or action of the sphincter muscle that would convert the two ducts into a continuous channel was very small, and concluded that the reflux of bile as a factor in the production of pancreatitis is minimal so that we must look elsewhere for the cause in most cases of pancreatitis.

The gall-bladder with its concentrating function, is in part a storage chamber. Thirty cubic centimeters per hour is the average amount of bile secreted, which may be increased or decreased according to the amount and kind of stimulation present. Four hundred and twenty cubic centimeters are secreted in the interval between digestion and this being concentrated ten times, can readily be stored in the gall-bladder.

Leeds believes the gall-bladder adds a hormone which increases bile formation.

In the past it was believed by some that the gall-bladder possessed a hormone which stimulated HCl secretion. However, this is not borne out clinically. In studying 100 operative cases of gall-bladder disease in which a gastric analysis preceded the operation, no definite conclusion could be arrived at concerning hyper- or hypo-acidity, with reference to the cholelithiasis or cholecystitis. It is true that acid values are lower in some cholecystectomized patients, however, no conclusion can be drawn from the same, because gastric acidity is a variable factor, and no rule can be applied to it.

Although much progress has been made as regards gall-bladder function, continued experimentation is needed to determine what other part it plays in the biliary system, and what harm, if any, occurs from its removal.

5. Is "B" BILE GALL-BLADDER BILE?

A greatly disputed point among men interested in medical biliary drainage, is whether the dark bile called "B" bile is in reality gall-bladder bile.

Lyon originally separated his aspirations into three types of bile, "A" bile, duct bile; "B" bile, gall-bladder bile; "C" bile, liver bile. This naturally was merely an arbitrary division and not meant to be construed literally.

This division largely depends on a color change and microscopical sediments, hence there naturally must be a mixture of various types of bile in all specimens. "A" bile is never just duct bile, but a mixture of duct bile and liver bile, and likewise "B" bile is never just gall-bladder bile, but a mixture of liver bile and gall-bladder bile. The gall-bladder never empties itself completely, and usually sends out small spurts of bile. The amount expelled by the gall-bladder varies greatly and depends entirely on the force exerted on it, or by it. The "B" fraction is never wholly gall-bladder bile, and represents only the gall-bladder fraction, or in other words, that part of the drainage which contains some of the gall-bladder bile or elements.

If 1 cc of ink is added to 20 cc of water, the mixture is naturally a dark colored fluid, if 4 cc of ink are added to the above amount of water, the mixture is a darker one, and so it is in all probability with "B" bile, that is, "B" bile being a mixture of gall-bladder bile and liver bile.

In reading color changes, no two laboratories agree, and for that reason interpretations of "B" bile will necessarily be a variable factor. "B" bile should not only be dark but likewise have the qualities of "B" bile, namely increased mucus, cholesterin crystals, pigmented columnar cells, etc. Color changes must be observed through the glass window in the duodenal tube, and not taken after the bile has been standing, because it is a well known fact that bile pigments oxidize when exposed to light and air.

In some cases of medical biliary drainage, the duodenal tip will itself produce a relaxation of the sphincter of Oddi, and three types of bile can be obtained. No chemical agent being used, the darker or "B" bile in all probability represents the gall-bladder fraction, because it is in the gall-bladder that the darker pigment is found. Meyer and Einhorn were the first to use this method, and regard that duodenal contents in fasting cases are of great value in biliary diagnosis.

Gall-bladder bile is undoubtedly used for digestion, hence the gall-bladder must empty part of its contents at some time during digestion. It is easy to prove that gall-bladder contents reach the intestine, hence it seems logical to suppose that a part of it can be obtained in a biliary drainage.

Experiment I. September 16, 1922. A white male dog, weighing 18 pounds, anesthetized with ether at 9.45 A.M. Abdomen opened under aseptic conditions at 10.00 A.M. and 4 cc of carmine dye were injected into the gall-bladder. Abdomen closed. At 12.30 P.M. dog was up and about and in excellent condition. No food given this day, but water *ad lib*. September 17, 1922, there was evidence of several bowel movements during the night, but no dye was detected. A feeding of beef, chicken bones, and bread was given, which he ate readily. September 18, 1922, there were new stools of hardened consistency which contained a reddish pigment. The dog was now killed by a massive dose of strychnine (intracardially).

Autopsy. Abdomen opened. Gall-bladder more reddened than normal. Gall-bladder still contained considerable dye and bile, about 6 cc. Stomach empty, duodenum empty. No stain about ampulla. At a distance of 24 cm. distally, the dye was mixed with the fluid contents of the bowel. This continued into the large bowel. Several pieces of inspissated feces taken from rectum showed our dye intermixed with the same.

Conclusion. Dye found in feces forty-eight hours after its injection into the gall-bladder showing that part of the gall-bladder contents are expelled sometime during digestion.

A number of men have injected dye into the gall-bladder of dogs and tried to recover the same by douching the duodenum with magnesium sulphate.

Crohn *et al*, report that they were unable to recover the dye in their dog experiments except in one. In this experiment the dye was obtained only after faradic stimulation of the peripheral end of the right vagus, which caused general contractions of the abdomen, stomach and intestines. However, this shows that gall-bladder bile can be obtained whether it be by external factors, gall-bladder contraction, or a combination of both.

Johnson of Cleveland, in dog experiments, obtained three types of bile in normal dogs, and not in cholecystectomized dogs.

Graham, in dog experiments, was able to recover dye injected into the gall-bladder of dogs when position or gravity was used, and concludes that the so-called "B" fraction in non-surgical biliary drainage, is in part, at least derived by gravity from the gall-bladder.

Welch, *et al.*, of Lincoln, reports an experiment in which they recovered the dye from the gall-bladder of a dog, by use of magnesium sulphate.

In our own experiments, we were able to recover the dye injected into the gall-bladder in three instances. We used decerebrated dogs because in this manner anesthesia was eliminated and we were dealing with a living automaton.

Experiment II. Black female dog, ether anesthesia at 12.30 P.M. Carotids tied at 12.48 P.M. Decerebrated at 1.00 P.M. Dog in good condition at 1.30 P.M. Abdomen now carefully opened and tube passed per orum into stomach, then into duodenum and sutured at 2.15 P.M.; 5 cc of neutral red solution injected into gall-bladder. At 2.20 P.M., 25 cc warm magnesium sulphate injected into duodenum through duodenal tube. This returns light yellow. At 2.25 P.M., fluid assuming a reddish color; at 2.30 P.M., fluid deep red; at 2.46 P.M., fluid still red; at 3.05 P.M., fluid still red; at 3.15 P.M., fainter red. Carotid pressure registering 100 mm. of Hg. At 3.30 P.M., 15 cc of magnesium sulphate again injected obtaining a light yellow fluid. No further evidence of dye followed.

Autopsy (at 4.00 P.M.). First portion of duodenum unstained. Beginning about 2 cm. above ampulla, the mucosa was markedly red and stained for a distance of 115 cm. distally with a bright red color. Gall-bladder not empty; 8 cc of bile intermixed with dye still present.

Conclusion. spurts of gall-bladder bile do occur. Gall-bladder does not completely empty.

Experiment III. A tanned mongrel, weighing 63 pounds. Ether anesthesia at 11.00 A.M. Carotids tied at 11.30 A.M. Decerebrated at 12.00 M. Abdomen opened at 12.30 P.M. Dog in good condition. Duodenal tube passed and tip sutured just beyond pars pylorica. Gall-bladder distended. Four cc of dye injected into gall-bladder at 1.15 P.M. At 1.20 P.M., jejunum opened and no dye present. At 1.25 P.M., 33 cc of 33 per cent magnesium sulphate injected through duodenal tube; 10 cc syphoned out. Jejunum closed by sutures and abdomen carefully closed. Drainage poor on account of high position of duodenal tip. At 2.45 P.M., abdomen was opened, and no marked change in size of gall-bladder found. Dog killed by gas.

Autopsy. Stomach and first portion of duodenum unstained. Ampulla deeply stained, and for some distance distal to it.

Conclusion. The tube was placed too high, and a poor drainage resulted. The dye was present at ampulla and distal to it, showing that at least some dye was expelled but gall-bladder not empty.

Experiment IV. Black female dog, weighing 60 pounds. Anesthetized 10.45 A.M. Carotids tied 11.10 A.M. Decerebrated 11.25 A.M. Dog in good condition 11.40 A.M. Abdomen opened 11.45 A.M., and duodenal tube passed in usual manner. Gall-bladder distended. Dye injected into gall-bladder, and abdomen carefully closed. At 11.50 A.M., duodenum douched with 20 cc warm water, returned bile stained; 12.10 P.M. drainage still light yellow; 12.15 P.M., 30 cc of warm 33 per cent magnesium sulphate injected; 12.30 P.M., drainage light yellow; 12.50 P.M., drainage light yellow. Duodenum now douched with 200 cc warm distilled water. At 1.05 P.M. bile drainage more freely, and slightly tinged with red; 1.20 P.M. drainage deep red; 1.30 drainage still red; 2.35 drainage, stain much lessened. Dog killed at 2.45.

Autopsy. Abdomen opened. Gall-bladder more flaccid, but not empty. Bile intermixed with dye. Stomach negative. First portion of duodenum negative; ampulla and 13 cm. beyond heavily stained.

Conclusion. Magnesium sulphate does not act as a specific hormone. Large amount of warm water obtained dye. Gall-bladder not empty.

In all of the foregoing experiments, great care was taken not to handle the gall-bladder, and no manual pressure was exerted on it.

Experiment V. Black male dog, weighing 52 pounds. Anesthetized with ether at 1.50 P.M. Carotids tied at 2.15 P.M. Decerebrated at 2.20 P.M. Dog in good condition at 3.15 P.M. Abdomen opened at 3.20 P.M. Duodenal tube introduced at 3.25 P.M., stitching duodenal tube in place. Gall-bladder moderately distended. Aspiration revealed small amount of blood-stained material. Five cc of stain injected into gall-bladder. Abdomen closed at 3.30 P.M.; aspiration reveals several cubic centimeters of grayish fluid, no bile being present; 3.35 P.M. 400 cc of warm magnesium sulphate (33 per cent) injected through duodenal tube. At 3.48 P.M., clear yellow fluid aspirated through duodenal tube; 3.55 P.M., clear yellow fluid; 4.10 P.M., clear yellow fluid; 4.20 P.M., restimulated with magnesium sulphate; 4.35 P.M., clear yellow fluid; 4.40 P.M., duodenum opened and small amount of bile-stained fluid present. No evidence of dye found. Dog now killed.

Autopsy. On opening abdomen, no apparent increase or decrease in size of gall-bladder found. No evidence of dye injected into gall-bladder in any part of intestinal tract. Stain still in gall-bladder. No obstruction present.

Conclusion. Apparently no increase or decrease in size of gall-bladder found. Free flow of bile; no change of pigments apparent. No evidence of dye found, showing duct sphincter may be relaxed and no gall-bladder elements present.

Experiment VI. White female dog. Dog anesthetized at 2.30 P.M. Carotids tied at 2.45 P.M. Decerebrated 3.00 P.M. Dog

in good condition at 3.15 P.M. Abdomen opened at 3.20 P.M. Gall-bladder moderately distended. Two cubic centimeters of stain injected into gall-bladder. Duodenum brought forward and anchored. Duodenum opened, but at no point could we find any evidence of bile, nor did any flow from the ampulla. At the end of ten minutes, 20 cc of warm magnesium sulphate was poured into region of ampulla. In ten minutes bile began to flow at irregular intervals of ten seconds, twenty-seven seconds, thirty-two seconds, and five seconds, keeping this irregular rate over a period of four minutes, at about four ejections per minute. Repeated applications of magnesium sulphate failed to cause any visual change in size of gall-bladder and no dye ejected.

Conclusion. No emptying of gall-bladder, nor presence of dye noted. Intermittent spurts of bile were visible, but no change of pigments occurred.

Experiment VII. Airedale, weight 40 pounds. Dog anesthetized at 10.45 A.M. Carotids tied at 11.20 A.M. Decerebrated at 11.30 A.M. Abdomen opened at 11.45 A.M., and duodenal tube stitched in place. This dog had been given no food for forty-eight hours, but was allowed water *ad lib.* Visual examination of the gall-bladder showed it to be more distended than that of any other dog. Dye injected into gall-bladder at 11.50 A.M. Duodenum now douched with 30 cc warm water. At 12.10 P.M. clear grayish fluid returned. No stain nor bile present. At 12.15 P.M., irrigated with 20 cc warm distilled water. This returned bile stained, but no dye was present. At 12.30 P.M. drainage still light yellow; 12.40 P.M. duodenum douched with 35 cc warm magnesium sulphate (33 per cent); 12.45 P.M. drainage still light yellow; 1.05 P.M., restimulated with magnesium sulphate; 1.20 P.M. drainage continued light yellow fluid; 1.30 P.M. duodenum irrigated through tube with 200 cc warm distilled water. Drainage continued light yellow color; 1.45 P.M. abdomen opened and duodenum opened. No evidence of dye was present. At 1.50 P.M., $\frac{1}{100}$ grain of eserine sulphate injected. No effect on gall-bladder noted. At 2.10 P.M., 1 per cent HCl washed over duodenum, which was followed by puckering of mucosa and ampulla.

Autopsy. Negative.

Conclusion. Fasting dog presented distended gall-bladder; no emptying of gall-bladder, and no dye ejected with use of eserine.

From the foregoing experiments, it seems possible at times to recover stain from gall-bladder injected with dye, and at times not. We did not use gravity as Graham did, and hence probably had more negative results. However, we believe that "B" bile is in part gall-bladder bile, because dye injected into the gall-bladder was recovered in three experiments, and where no dye was found, no change in pigments occurred. We also believe that at times gall-bladder bile may be obtained, and at times no gall-

bladder bile may be obtained with no apparent obstruction. Hence, care must be exercised before diagnosing obstructions of the cystic duct.

6. IS THERE A CHEMICAL CHANGE WHICH CAN ACCOUNT FOR THE DARK "B" BILE, OR, IN OTHER WORDS, AN OXIDATION OF PIGMENTS?

The chemistry of bile pigments is still in its infancy, and a great deal more work is needed before we will know all about oxidation and reduction of bile pigments.

Einhorn is of the opinion that the "B" fraction in a biliary drainage is a chemical change and bears no relationship to gall-bladder contents. He believes that it is the sulphate radical excreted by the liver which produces the darker bile.

Dunn and Connell claim it is the magnesium ion carried to the liver by the portal blood acting as a cholagogue producing a bile flow rich in pigment, or that it is the destruction of red cells by the magnesium ion somewhere in the portal system resulting in a sudden dumping of an increased quantity of blood pigment on the liver, which reacts by an increased output of bile rich in pigment. They also doubt "B" bile being gall-bladder bile on account of obtaining three types of bile in a case where the gall-bladder was out and the ducts destroyed.

Rous and McMaster, in experimental work on dogs, found that as long as the gall-bladder or any part of cystic duct was left, the bile remained pigmented, but if the gall-bladder and cystic duct were entirely removed, no pigmented bile remained, and the so-called white bile of surgeons was found.

In some later work, they found that in bile secreted against abnormally high pressure, as during partial obstruction, the pigment, cholate and cholesterol outputs are all cut down, and so much more is the fluid bulk that the concentration of substances per cubic centimeter of bile is notably lessened. They coin a new term "hydrohepatosis." They also believe in the existence of an enterohepatic circulation of pigment.

Chester M. Jones, in his work on bile pigments, found no relationship between the amount of magnesium sulphate given and bile pigments formed and also believes from his work that "B" bile is a mixture of gall-bladder bile and liver bile.

We do not believe that the sulphate radical or the magnesium ion bears any relationship to the dark pigment obtained in medical drainages. We also do not believe that the magnesium ion causes such a rapid destruction of red cells.

In test-tube experiments we have found that:

- (a) Magnesium sulphate plus yellow ox bile : : No change in pigment.
- (b) Alkali plus yellow ox bile : : No change in pigment.
- (c) Alkali plus green ox bile : : Reduction in pigment.

(d) Acid plus yellow ox bile : : Change to green bile, oxidation of pigment.

(e) Acid plus green ox bile : : Change to dark green bile, oxidation of pigment.

(f) Yeast cells plus green ox bile : : Change in part to yellow bile, reduction of pigment.

(g) H_2S plus green ox bile : : Change to reddish bile, reduction of pigment.

(h) Air and light plus yellow ox bile : : Change to green bile, oxidation of pigment.

Gall-bladder bile is always darker than liver bile, which may be due to an oxydase being present in the gall-bladder, but this is not a proven fact. We do know however, that if the hydrogen-ion concentration of bile is shifted to the acid side, the resulting conditions are more favorable to oxidation of pigments.

According to McLeod, the pH of liver bile is 7.8, while the pH of gall-bladder bile is 5.3 to 7.4, that is, the H-ion concentration of bladder bile is higher than that of liver bile.

Dark or "B" bile may be obtained in medical drainages without any chemical agent being used, and the sphincter of Oddi may be relaxed by mere irritation of the metal tip, hence, this dark bile cannot be due to a chemical change and most likely is gall-bladder bile.

Warm distilled water will also bring forth spurts of dark bile and this also cannot be due to any chemical change.

Experiments VIII and IX. Two male dogs. Anesthetized with ether. The gall-bladder and bile ducts were exposed. A glass cannula was placed in the common duct, and 10 cc of a 25 per cent solution of magnesium sulphate was injected into portal vein. No change of pigments was noted in glass cannula over a period of forty-five minutes in either dog. If the magnesium ion could produce a destruction of red cells in the portal system it seems that magnesium sulphate injected directly into portal vein should also do so. However, in these two experiments no visible change of pigment could be noted.

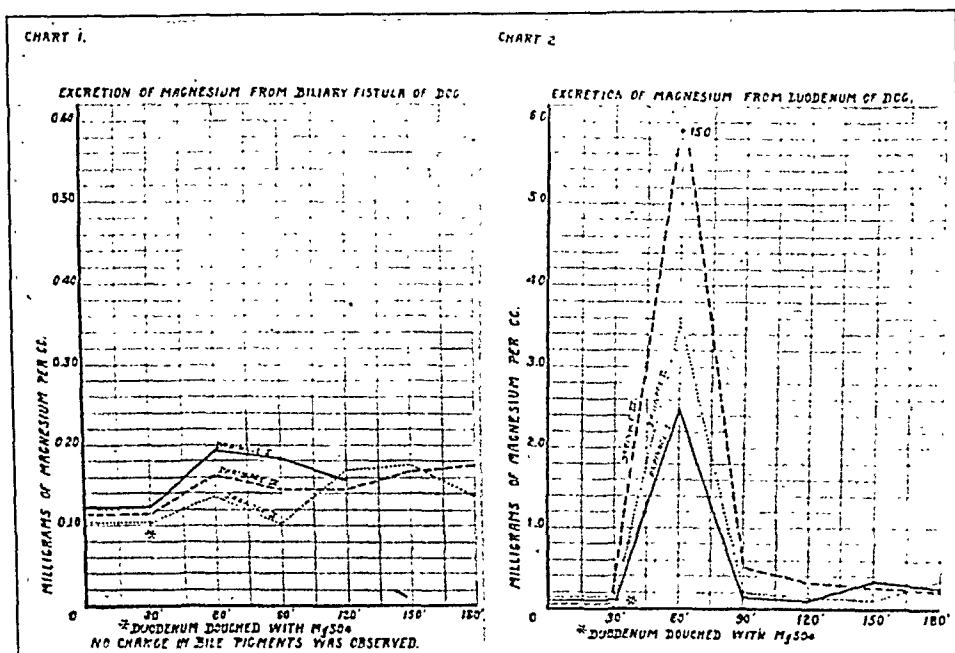
Various salts such as sodium sulphate, glucose, sodium bicarbonate, peptone, dilute hydrochloric acid, etc., all cause dark bile, hence it is hard to believe that they can all produce the same chemical change, or produce similar effects on pigments.

We have corroborated the findings of other men that magnesium can be absorbed and excreted by the liver. However, the excretion of magnesium bears no relationship to the type of pigment excreted. The large amounts of magnesium did not show the darker pigment. Hence, the sulphate radical or magnesium ion can bear no relationship to the dark pigment. This can be demonstrated by the following experiments, charts, and tables. The excretion of

magnesium was determined from a biliary fistula of a dog after instillations of magnesium sulphate into the duodenum.

The Drainages I, II and III shown by curves in Charts 1 and 2 and by figures in Table I, were done in the following experiments.

Experiment X. A medium sized white mongrel was anesthetized, a cholecystostomy and a Frank gastrostomy were performed. A small rubber tube was sutured in the gall-bladder and a duodenal tube was passed through the gastrostomy opening and anchored in the duodenum (linen suture used). The dog was given special care and progressed nicely.



Drainage I was on February 18, 1923; Drainage II was on February 19, 1923; Drainage III was on February 29, 1923. The drainage was done as follows: Drainage from the duodenal and gall-bladder tubes were collected separately in test tubes for a period of three hours, the tubes being changed every half hour. At the end of the first half hour 20 cc of a warm 33 per cent solution of magnesium sulphate were injected through the duodenal tube. This gave 12 specimens, 6 from the duodenum and 6 from the gall-bladder. The first 2 specimens were collected before the magnesium sulphate was injected, and were used as controls. The magnesium content of each specimen was determined by the method used by F. J. Tisdall and B. Kramer.¹

¹ Jour. Biochem., 1921, 48, 1.

TABLE I.—MAGNESIUM DETERMINATIONS.

Drainage I February 9, 1923 12.00-3.00 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	12.00-12.30	Brown	Alk.	1.10	1.0	0.1210	0.1210	0.1331
G. B. 2	12.30-1.00	Brown	Alk.	1.35	1.0	0.1936	0.1936	0.2013
G. B. 3	1.00-1.30	Brown	Alk.	1.25	1.0	0.1815	0.1815	0.2268
G. B. 4	1.30-2.00	Brown	Alk.	1.20	1.0	0.1573	0.1573	0.1887
G. B. 5	2.00-2.30	Brown	Alk.	0.40	1.0			
G. B. 6	2.30-3.00	Brown	Alk.	0.30	1.0			
Duod. 1	Yellow	Acid	18.0	1.0	0.1450	0.1450	2.6100
Duod. 2	Yellow	Neut.	38.0	1.0	2.5710	2.5710	97.6980
Duod. 3	Yellow	Neut.	13.0	1.0	0.1750	0.1750	2.2750
Duod. 4	Yellow	Acid	21.0	1.0	0.1270	0.1270	2.6670
Duod. 5	Yellow	Acid	16.0	1.0	0.2783	0.2783	4.4520
Duod. 6	Yellow	Neut.	6.0	1.0	0.1210	0.1210	0.7260

20 cc of saturated $MgSO_4$ injected into duodenum at 12.30 P.M.

Drainage II February 10, 1923 1.45-4.45 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.45-2.15	Brown	Alk.	3.6	1.0	0.1030	0.1030	0.3700
G. B. 2	2.15-2.45	Brown	Alk.	1.6	1.0	0.1390	0.1390	0.2224
G. B. 3	2.45-3.15	Brown	Alk.	1.3	1.0	0.1030	0.1030	0.1336
G. B. 4	3.15-3.45	Brown	Alk.	1.0	1.0	0.1690	0.1690	0.1694
G. B. 5	3.45-4.15	Brown	Alk.	1.3	1.0	0.1750	0.1750	0.2275
G. B. 6	4.15-4.45	Brown	Alk.	1.5	1.0	0.1390	0.1390	0.2085
Duod. 1	Yellow	Acid	24.0	1.0	0.1570	0.1570	3.7680
Duod. 2	Yellow	Acid	41.0	1.0	3.5500	3.5500	145.5500
Duod. 3	Yellow	Acid	6.0	1.0	0.1870	0.1870	1.1120
Duod. 4	Yellow	Neut.	10.0	1.0	0.1270	0.1270	1.2700
Duod. 5	Yellow	Acid	10.0	1.0	0.1090	0.1090	1.6900
Duod. 6	Yellow	Neut.	7.0	1.0	0.2760	0.2760	1.9320

20 cc of saturated $MgSO_4$ injected into duodenum at 2.15 P.M.

Drainage III March 1, 1923 1.35-4.35 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.35-2.05	Brown	Neut.	0.8	0.65	0.0785	0.1178	0.0970
G. B. 2	2.05-2.35	Brown	Neut.	1.2	1.0	0.1633	0.1633	0.1959
G. B. 3	2.35-3.05	Brown	Alk.	1.5	1.0	0.1452	0.1452	0.2178
G. B. 4	3.05-3.35	Brown	Neut.	2.0	1.0	0.1452	0.1452	0.2904
G. B. 5	3.35-4.05	Brown	Neut.	2.0	1.0	0.1694	0.1694	0.3388
G. B. 6	4.05-4.35	Brown	Neut.	1.8	1.0	0.1754	0.1754	0.3157
Duod. 1	Yellow	Neut.	1.0	1.0	0.0907	0.0907	0.5907
Duod. 2	Yellow	Neut.	36.0	1.0	15.0700	15.0700	542.5000
Duod. 3	Yellow	Neut.	16.0	1.0	0.5626	0.5626	9.0160
Duod. 4	Yellow	Neut.	34.0	1.0	0.3267	0.3267	11.1070
Duod. 5	Yellow	Neut.	22.0	1.0	0.2662	0.2662	5.8560
Duod. 6	Yellow	Neut.	12.0	1.0	0.1210	0.1210	1.4520

20 cc of saturated $MgSO_4$ injected into duodenum at 2.05 P.M.

Drainages IV and V shown by curves in Charts 3 and 4, and by figures in Table II, were done in the following experiment:

Experiment XI. A large white bulldog was operated upon, and handled exactly the same as in Experiment X. The methods we used were the same as in Experiment X.

Drainages VI and VII shown by curves on Charts 5 and 6, and by figures in Table III, are estimations of magnesium from human biliary fistulæ. These were taken on two separate patients in whom a cholecystostomy was needed. The duodenal tube was passed in the usual manner, and 50 cc of a 33 per cent magnesium sulphate solution was injected into the duodenum and the magnesium was estimated in a similar manner to Experiments X and XI.

Chart 6 shows only one curve, namely that of Drainage VI.

The magnesium of the duodenal drainage in Drainage VII was not estimated because the amount of magnesium sulphate returned through a duodenal tube is variable and it was deemed unnecessary.

In 2 experiments on human biliary fistulæ it was noted that when the duodenum was douched with magnesium sulphate and

TABLE II.—MAGNESIUM DETERMINATIONS ON DOG BILE.

Drainage IV April 5, 1923 8.30-11.30 A.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	8.30- 9.00	Brown	Alk.	6.0	2.0	0.4054	0.2027	1.2162
G. B. 2	9.00- 9.30	Brown	Alk.	2.0	2.0	0.5204	0.2602	0.5204
G. B. 3	9.30-10.00	Brown	Alk.	6.0	2.0	0.4780	0.2390	1.4340
G. B. 4	10.00-10.30	Brown	Alk.	4.0	2.0	0.4780	0.2390	0.9560
G. B. 5	10.30-11.00	Brown	Alk.	3.0	2.0	0.4296	0.2148	0.6444
G. B. 6	11.00-11.30	Brown	Alk.	4.0	2.0	0.4054	0.2027	0.8108
Duod. 1	.	Yellow	Neut.	1.0	2.0	0.3872	0.3872	0.3872
Duod. 2	.	Yellow	Neut.	10.0	1.0	18.9800	18.9800	189.9800
Duod. 3	.	Yellow	Neut.	1.0	1.0	1.3310	1.3310	1.3310
Duod. 4	.	Yellow	Neut.	0.5	0.5	0.5990	1.1980	0.5990
Duod. 5	.	Yellow	Neut.	1.0	1.0	0.7502	0.7502	1.1253
Duod. 6	.	Yellow	Neut.					

20 cc of saturated $MgSO_4$ injected into duodenum at 9.00 A.M.

Drainage V April 7, 1923 1.30-4.30 P.M.

	Time.	Color.	Litmus.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total mag., mg.
G. B. 1	1.30- 2.00	Brown	Alk.	5.0	2.0	0.3384	0.1691	0.8470
G. B. 2	2.00- 2.30	Brown	Alk.	6.0	2.0	0.5142	0.2571	1.5126
G. B. 3	2.30- 3.00	Brown	Alk.	4.0	2.0	0.4178	0.2239	0.8956
G. B. 4	3.00- 3.30	Brown	Alk.	4.0	2.0	0.3750	0.1875	0.7500
G. B. 5	3.30- 4.00	Brown	Alk.	5.5	2.0	0.4052	0.2026	1.1105
G. B. 6	4.00- 4.30	Brown	Alk.	5.5	2.0	0.3024	0.1512	0.8316
Duod. 1	.	Yellow	Neut.	2.0	1.0	0.3025	0.3025	0.6050
Duod. 2	.	Yellow	Neut.	5.0	1.0	17.2550	17.2550	86.2750
Duod. 3	.	Yellow	Neut.	1.5	0.7	2.5410	3.6300	5.4450
Duod. 4	.	Yellow	Neut.	1.0	0.8	5.2032	0.6504	0.6504
Duod. 5	.	Yellow	Acid	1.0	1.0	0.5022	0.5022	0.5022
Duod. 6	.	Yellow	Neut.	1.0	0.9	3.6297	0.4033	0.4033

20 cc of saturated $MgSO_4$ injected into duodenum at 2.00 P.M.

CHART 3

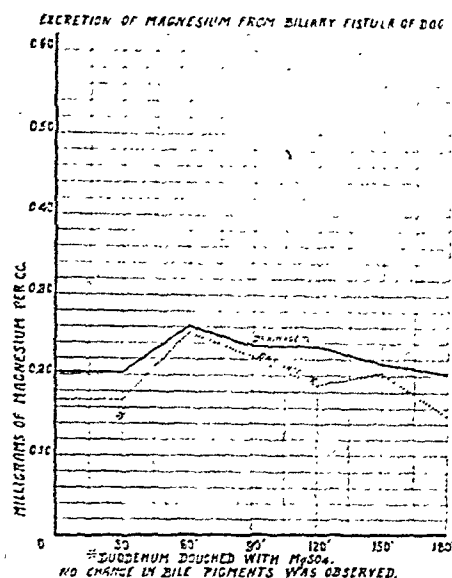


CHART 4

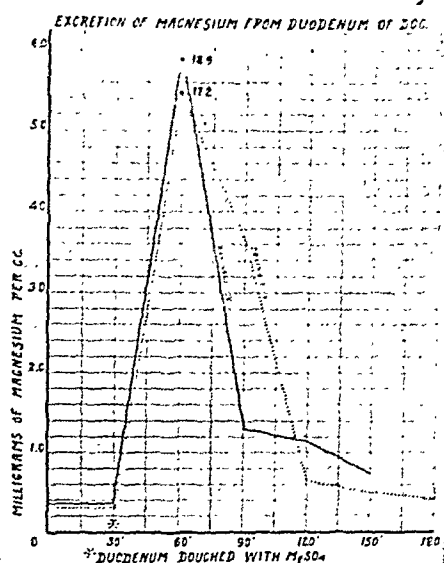


CHART 5

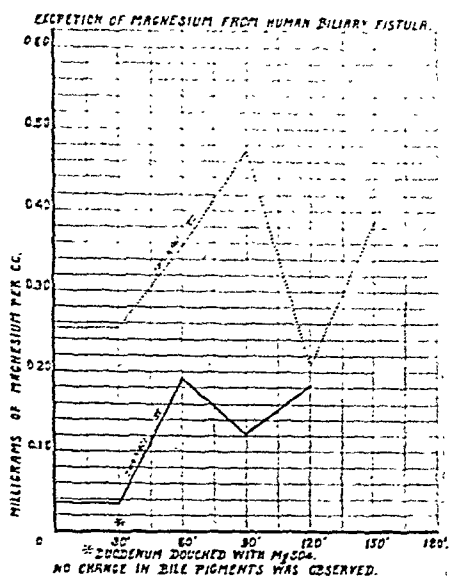
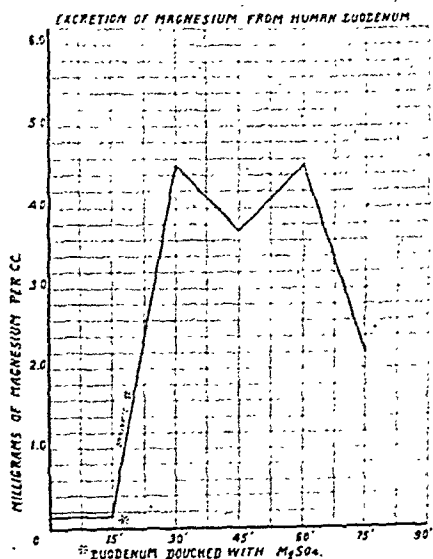


CHART 6



the bile drainage was free, the amount of biliary fistula bile decreased and then later again increased. This might be used as another point in favor of "B" bile coming from the gall-bladder. The figures are shown in Table III.

The bile pigments from the biliary fistulae in dogs or in humans showed no change after douching the duodenum with magnesium sulphate, in periods over two hours. It might be noted that pigments coming from biliary fistulae when freshly examined are lighter than bile pigments obtained from the gall-bladder at time of operation.

TABLE III.—MAGNESIUM DETERMINATIONS ON HUMAN BILE.

Drainage VI

	Time, min.	Color.	Volume excreted, cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total, mag., mg.
G. B. 1*	30	Brown	9.0	5.0	0.1815	0.0363	0.3267
G. B. 2	30	Brown	3.0	2.5	0.4840	0.1936	0.5808
G. B. 3	30	Brown	2.0	2.0	0.2420	0.1210	0.2420
G. B. 4	30	Brown	2.0	2.0	0.3630	0.1815	0.3630
Duod. 1*	15	Yellow	20.0	5.0	0.8470	0.1694	3.3880
Duod. 2	15	Yellow	42.0	5.0	22.6270	4.5254	190.0668
Duod. 3	15	Yellow	39.0	5.0	18.6340	3.7268	145.3452
Duod. 4	15	Yellow	12.0	5.0	22.0220	4.5044	51.0528
Duod. 5	15	Yellow	52.0	5.0	10.8450	2.1690	112.7880

Drainage VII

	Time, min.	Color.	Volume, excreted cc.	Quant. used for determ., cc.	Mag. in this amt., mg.	Mag. per cc, mg.	Total, mag., mg.
G. B. 1*	30	Brown	6.0	2.0	0.5082	0.2541	1.524
G. B. 2	30	Brown	3.5	2.0	0.7138	0.3569	1.249
G. B. 3	30	Brown	1.4	1.0	0.4719	0.4719	0.660
G. B. 4	30	Brown	4.0	2.0	0.4114	0.2057	0.822
G. B. 5	30	Brown	1.0	0.9	0.3484	0.3872	0.430

Drainage VIII

	Time, min.	Color.	Volume excreted, cc.
G. B. 1*	30	Brown	9.0
G. B. 2	30	Brown	1.0
G. B. 3	30	Brown	7.0
G. B. 4	30	Brown	5.0
Duod. 1*	15	Yellow	15.0
Duod. 2	15	Yellow	45.0
Duod. 3	15	Yellow	41.0
Duod. 4	15	Yellow	18.0

COMPOSITION OF HUMAN BILE.
Parts per 100.

	Bladder bile.	Fistula bile.
Water	82.97	97.02
Solids	17.03	3.98
Bile salts . . .	9.70	1.01
Mucin and pigment	4.19	0.48
Cholesterol . .	0.99	0.26
Fat	0.19	0.68
Soaps	1.12	0.26
Lecithin	0.22	0.64
Inorganic salts .	0.51	0.92

* Duodenum douched with $MgSO_4$.

We believe from the foregoing experiments that the magnesium ion or sulphate radical has no relationship to "B" bile.

Since our present knowledge of oxidation and reduction of bile pigments is still meagre, it seems to us most logical to assume that "B" bile or the dark pigment, comes from the gall-bladder. Oxidation and reduction undoubtedly are a variable factor and the future may throw more light on this most interesting problem.

7. IS ALL DARK COLORED BILE "B" BILE?

All dark bile is not "B" bile because we may get a slight change in pigments from dilated ducts, or stasis in the liver after the gall-bladder has been removed. This bile however, is not typical "B" bile, having less mucus and no gall-bladder elements, hence,

all dark bile is not "B" bile. The oxidation of pigments has been previously discussed, and need not be repeated at this time.

8. DOES MAGNESIUM SULPHATE HAVE SPECIFIC ACTION, OR CAN OTHER SUBSTANCES LIKEWISE CAUSE SPHINCTER RELAXATION?

This question has been answered with the other questions, earlier in the paper. Magnesium sulphate in our opinion, has no specific action, however, it relaxes the sphincter better than any reagent we have used. Magnesium sulphate, sodium sulphate, olive oil, dilute HCl, peptone, warm water, the duodenal tip, etc., may all cause sphincter relaxation.

McWhorter has demonstrated that a 25 per cent solution magnesium sulphate applied to the duodenum will reduce the resistance of the sphincter of Oddi, 50 to 100 mm. of water.

9. IS MEDICAL BILIARY DRAINAGE OF ANY AID DIAGNOSTICALLY?

Most men agree that the examination of duodenal contents is of some value, hence biliary drainage must be of some value. Examination of any of the body secretions or excretions are of value, and this method affords the simplest way in which to recover bile for examination.

There is a great difference of opinion on the value of bile examination, yet the most radical must agree that if it tells nothing more, it will inform us as to the patency of the common duct. Gall-bladder diagnoses are often difficult, and any slight assistance may at times be of great value. It is impossible for the surgeon to lightly palpate or inspect a gall-bladder in an opened abdomen and say it is normal, for oftentimes on opening it, pathology is found, hence any method that will even slightly aid in diagnosis is of value. Early disturbances of liver function are also difficult to recognize, however, recently the work with phenoltetrachlorophthalein promises to be a great aid.

In our opinion, a good history is the most essential factor in making biliary diagnosis. The next in order is a careful physical examination, then the roentgen-ray and lastly the laboratory.

The profession is now justly reacting against using laboratory measures to the exclusion of good, common-sense, careful histories and physical examinations. There is no question that all methods at our disposal should be used and the laboratory at least should play a part in the routine of examinations, hence the examination of bile is also of value.

The examination of bile may be an aid, and yet it is not absolutely essential in all cases of biliary diagnosis. This however, is true of urine analysis, sputum analysis, and gastric analysis. If the duodenal contents are examined carefully before using magnesium sulphate and not many leukocytes are found, then after relaxation of the sphincter with magnesium sulphate many pus cells are found, we are justified in assuming biliary infection is present.

It is sometimes necessary to beware of being ultra-scientific and

trying to make hair splitting diagnosis for in most instances if checked up, the diagnosis is wrong. We feel that if it is possible to decide whether a gall-bladder is one for surgical or medical treatment, we have performed our duty.

Many men have apparently diagnosed obstructions of the cystic duct by this method, and oftentimes one can suspicion it after repeated stimulations with magnesium sulphate and no "B" bile being obtained. However, with our experimental and clinical observations to date, we feel that great caution should be exercised before attempting it, because there are many anomalies and pitfalls that may confuse us. If there is a definite obstruction of the cystic duct, the case is surgical, and we feel it better to diagnose our cases as such.

Cultures in our opinion are of definite value in some cases and we believe this fact can no longer be doubted. If cultures are carefully taken and proper attention is paid to the proper technic, it undoubtedly is an aid in location of focal infection. If two or three duodenal cultures are negative, and then after magnesium sulphate stimulation a relaxation of the sphincter of Oddi occurs and a bile culture is taken and proves a positive streptococcus on two or more cultures, then we are justified in placing the infection in the biliary tract.

If after a cholecystectomy the patient is not cured, and a positive culture is obtained, it immediately informs us that the ducts are still infected.

By cultural methods in biliary drainage, typhoid carriers may be detected, and hence it is of decided value.

The significance of cholesterin crystals is another interesting problem. The gall-bladder undoubtedly contains more cholesterin than any other organ of its size, and finding an increased cholesterol content of "B" bile is another point in favor of "B" bile being gall-bladder bile. The relationship of the cholesterin of the blood and the cholesterin content of the gall-bladder is still a disputed point. An increased cholesterol content in the blood with gall-bladder symptoms is regarded by some to be in favor of cholelithiasis. However, others doubt the value of this laboratory finding.

It is true that many gall-stones are cholesterin stones, but whether or not cholesterin crystals of themselves denote gall-stones, is a purely hypothetical assumption. One may find many cholesterin crystals in a biliary drainage, and yet at operation no stones are found. However, if many crystals are found, and the other symptoms coincide, it may sway the balance in favor of stones.

We feel that macroscopical blood and little or no bile on stimulation with magnesium sulphate in connection with other physical signs aids us in the diagnosis of malignancy of the ampulla of Vater.

Palefski has used the duodenal tube as a method of visualization

of the duodenum, and thinks a distorted curve denotes evidence of periduodenal adhesions.

Biliary drainage aids in the diagnosis of certain types of headaches. This method affords great relief in biliary headaches, and hence is an aid in their diagnosis.

To summarize, it is our opinion that the diagnostic values of biliary drainage, are as follows:

- (a) It gives definite information as to the patency of the ducts.
- (b) It aids in diagnosis in some cases of malignancy, especially of the ampulla of Vater.
- (c) Real dark thick bile denotes biliary stasis.
- (d) Positive cultures denote biliary infection, and are another means of locating foci of infection.
- (e) It aids in locating some typhoid carriers.
- (f) In postoperative cases, with return of symptoms, it determines the patency of the ducts, and whether or not infection is still present.
- (g) Gall-bladder sand may aid in the diagnosis of stones. However, we have not observed this as often as reported by others and consider it of little value.
- (h) It aids in the diagnosis of pancreatitis.
- (i) It is of value in duodenal visualization.
- (j) It assists in differential diagnosis of right upper quadrant lesions.
- (k) It aids in the diagnosis of certain types of headaches.

10. IS MEDICAL BILIARY DRAINAGE OF ANY VALUE AS A THERAPEUTIC PROCEDURE?

Biliary drainage, as a therapeutic agent, has its limitations, but if used rationally, it is undoubtedly of great benefit in many cases.

Surgery is still the preferable means of attack in most biliary lesions, and will continue so, because infections of the gall-bladder are mostly submucosal and in the wall, hence medical drainage will not relieve the infection as well as surgery.

Medical biliary drainage offers some cures in biliary lesions, however, it is more of a palliative procedure than curative.

Some men claim that its value is purely psychic, and no real pathology can be relieved. It has undoubtedly a great psychic factor, but this alone cannot explain the real benefits obtained by all cases. It will be impossible in this paper to cite a long list of cases, but the literature is so full of beneficial results reported by good men, that there can be no question that it has some value.

We often forget that our patients come for relief of their suffering, and if medical drainage relieves them, whether it be psychic or otherwise, our beneficial result is obtained.

We believe medical biliary drainage is indicated in the following cases:

- (a) In cholecystectomized patients with return of symptoms.
- (b) In catarrhal jaundice.
- (c) In biliary headaches.
- (d) In cases where surgery is contraindicated: (1) old people;
- (2) heart cases; (3) diabetics.
- (e) It aids in clearing up typhoid carriers.
- (f) It is of value in pre- and postoperative treatment of biliary infection.
- (g) It benefits so-called biliousness and lethargy.
- (h) It aids in treatment of pancreatitis.
- (i) It benefits enteroptotizers with pain in the upper right quadrant. (This may be psychic.)
- (j) It assists in preventing postoperative vomiting.

11. IN WHAT MANNER IS BILIARY DRAINAGE OF VALUE AND WOULD GASTRIC LAVAGE AFFORD AS MUCH RELIEF AS BILIARY DRAINAGE?

We feel that biliary drainage assists in ridding the body of toxic material because duodenal lavage is of value in any toxic condition and has been recommended in toxemias of pregnancy.

It is an excellent aid because it increases the flow of bile. By increasing the flow of bile it must assist Nature in ridding itself of infection as well as of toxemia.

It indirectly flushes the liver, if one may use this crude expression, by drawing off more fluid from the liver, hence more fluid must of necessity be attracted toward the liver.

It acts as a temporary drain to the biliary passages and liver similar to a surgical drainage, hence assists in relieving infection.

By its catharsis it also rids the colon of stasis.

It is of great psychic value. The psychic side of a patient is frequently overlooked by many medical men, therefore oftentimes failures are present when success could be obtained.

Some claim that magnesium sulphate by mouth is just as efficacious as biliary drainage, however, anyone using biliary drainage in an unprejudiced manner over a long period of time, knows that it is lack of experience that prompts this statement.

Let us not condemn any method of procedure until you have given it a fair and unprejudiced trial. Likewise, do not recommend a simple procedure as a cure-all for any condition. Weigh each side carefully and then let experience be your guide.

We do not feel hyperenthusiastic about medical biliary drainage, for it has its limitations, yet if used conservatively and properly it undoubtedly is of value.

Summary. The gall-bladder does contract, however, its contraction power is minimal. The gall-bladder and the common duct sphincter are probably regulated by a definite reflex mechanism; however, more proof is needed before it is an accepted fact. Gall-bladder contraction alone does not empty the gall-bladder and

other external factors assist in expelling part of its contents. "B" bile is in part gall-bladder bile. The gall-bladder is more than a mere reservoir and undoubtedly has definite function even though these functions are not essential to life. The chemistry of bile pigments is still in its infancy. However, the action of the magnesium ion or the sulphate radical on the liver does not explain the dark bile, and likewise the magnesium ion does not cause a large destruction of red cells in the portal system producing a dark colored bile more rich in pigments. Slight changes in bile pigments may occur in cholecystectomized patients. Magnesium sulphate does not act like a hormone for other substances have like action. Biliary drainage is of some value diagnostically, but in a more limited way than expressed by some writers. In our opinion it is of no value in differentiating cholecystitis from cholelithiasis. It is an aid in locating infection in some cases of biliary disease. It is also a well known fact that gall-bladder bile is often sterile and hence a positive culture will not definitely localize, which part of the biliary tract is involved. It is of more value in determining if infection is still present in cholecystectomized patients. Biliary drainage is of more value as a therapeutic adjunct than as a diagnostic agent. It is curative in mild cases; however, it is to be used more as a palliative measure than a curative agent. Surgery is our best means of attack in most biliary infections. Biliary drainage has definite therapeutic value other than being a mere psychic aid.*

THE KOLMER MODIFICATION OF THE COMPLEMENT-FIXATION TEST FOR SYPHILIS: ITS RELATION TO THE CLINICIAN AND TO THE REQUIREMENTS FOR A STANDARD TECHNIC.†

BY ROBERT A. KILDUFFE, A.B., A.M., M.D.,
LOS ANGELES, CALIF.

(From the Laboratories of the Pittsburgh Hospital.)

A GREAT deal of water has passed under the bridge since Wassermann, in 1906, described the complement-fixation test for syphilis commonly known by his name, although, strictly speaking, the name is practically the sole remaining vestige of the method originally described.

* The references, ninety-one in number, are omitted from this article on account of lack of space but will be found in the author's reprints.

† Read before the Second Annual Convention of the American Society of Clinical Pathologists, San Francisco, June 26, 1923.

Probably no other single laboratory test has been subjected to more extensive and intensive investigation than this procedure, and while the preponderance of the literature was, in the beginning, largely the result of studies in laboratory technic and the product of the serologist, present studies are more properly the combined or, at least, the correlated production of serologist and clinician working in unison. This, beyond cavil, is as it should be, for while studies leading to refinements and perfection of technic are of value, their value is in direct proportion to, and directly determined by, the acid test of clinical interpretation and evaluation. Neither by serologist nor by the clinician working alone can the ultimate dictum be laid down; only as a result of the close and sustained coöperation of both can the final word be said as to the relative merits of this or that method of technic.

It is essential, therefore, that in the evaluation of any new method for performing this test, and particularly when the method is proposed as a standard technic for general adoption, that the study be not confined solely to the laboratory but conducted with the close coöperation of the clinician upon whose shoulders the responsibility for the interpretation of the reaction finally falls. This is especially necessary because syphilis, on account of its prevalence and the protean character of its manifestations, is a condition the recognition and handling of which is, in the main, not relegated to those especially trained or particularly interested and adept, but is rather a condition continually confronting the man in general practice; and it is upon his recognition of the infection that the ultimate success or failure of treatment in no small measure depends.

Any method to succeed as a claimant for general adoption, in the study of this disease, therefore, must be judged not alone by its feasibility in the laboratory; not alone by its value when interpreted by the specially trained expert; but in terms of its value to the practitioner in general; for, rightly or wrongly, momentous decisions will, at times, hang upon the result of an isolated serological examination. It is not the purpose of this communication to discuss the inadvisability of such an undue reliance upon the results of a single test; that has been done elsewhere^{1 2} and by many writers. It is purposed, rather, to consider the requirements to be fulfilled by a standard technic with particular reference to those formulated by the clinician.

To this end a series of slightly over 2000 tests will be considered from these standpoints, but, just as it is impossible to study satisfactorily the complement-fixation reaction from the laboratory standpoint alone, so it will be impossible to study this series from the clinical angle alone, for both are interrelated and both will be deciding factors of importance in determining the adoption of a standard technic.

The sera comprised in this series include those subjected to

routine examination in a variety of conditions in the medical, surgical, gynecological, and obstetrical wards of the Pittsburgh Hospital; sera sent in for diagnosis; sera from known syphilitics under treatment; and sera from "Morals Court" cases secured by Dr. A. H. Eggers, County Medical Inspector, Pennsylvania State Department of Health, and comprising a large number of prostitutes and persons of ill repute, many of whom were syphilitics under treatment. In addition to these, 104 cases of tuberculosis in all stages were subjected to a Wassermann test by the Kolmer modification, these last being secured through the courtesy of Dr. Joseph Shilene. To these gentlemen, and particularly to the Chiefs of Staff of the Pittsburgh Hospital, sincere acknowledgment is due for their unfailing coöperation. All sera were tested in exact accordance with the technic as described by Kolmer.^{3 4}

Analysis of the Series in Relation to the Requirements for a Standard Technic. I. SIMPLICITY OF TECHNIC.—As pointed out by Kolmer,⁵ and as is obvious, simplicity must be looked upon as a relative term when used in connection with complement-fixation reactions. Any method will present complexities to the inexperienced and inadequately trained worker—who should not be permitted to conduct even the simplest such test if it is to be done merely by "rule of thumb"—whereas, to the experienced serologist, or even to one not overburdened with experience but whose preparatory foundation has been well grounded, the Kolmer modification will present no manipulative difficulty. It will require care and attention, as will any method, while skill and rapidity in its execution are a matter of practice and grow with experience.

From the standpoint of its feasibility in a technical sense the conclusions drawn from practical experience with the method are entirely favorable and the test conforms to this requirement for a standard method. This conclusion is further confirmed by the fact that in none of the reports so far made concerning this method has any criticism been made of it from the standpoint of manipulative difficulty.

II. ECONOMY OF MATERIALS.—This is a matter of importance, not only in laboratories performing large numbers of tests, but also in those utilizing the method in a relatively small number. It is met in the Kolmer modification by the use of preserved complement which, preserved either by the use of sodium chloride (0.3 gm. to 1 cc of serum), or of sodium acetate, (1.5 parts of 12 per cent aqueous solution to 1 part of complement serum), will retain its activity for at least four weeks.

It is important to bear in mind, however, that the *fixability* of complement begins to show deterioration before its hemolytic activity is impaired and that, therefore, it is imperative that a known positive control be always included in the set-up. As an added precaution, it is my practice never to use a complement when more

than two weeks old; in an active laboratory, the serum will generally be used up before the expiration of this time.

While the initial expense of preparing the new antigen used in conjunction with the test⁶ is probably increased over that of ordinary methods, the resulting extract is so stable and so extraordinarily antigenic, thus permitting its use in small quantities and over long periods of time, that, in the end, it is probably cheaper than the continued maintenance of a supply of various extracts. As a maximum of 0.3 cc of serum and 1.5 cc of spinal fluid—quantities easily obtained—are sufficient for the performance of the quantitative reaction, from the standpoint of economy in materials, therefore, the method also qualifies as a standard technic.

III. ECONOMY OF TIME.—Here, having a primary incubation period of twelve to eighteen hours (thus requiring two days before a report can be made) the method presents a distinct variance from accustomed procedure.

It becomes necessary, therefore, to inquire, first, if the rendering of reports within a few hours is an essential feature of a standard technic from the standpoint of either serologist or clinician, and, second, if such rapid reporting is an actuality in practice?

As to the serologist, the increased time is a matter of little moment. The addition of the hemolytic system and the secondary incubation is a small thing on the second day and the added confidence in the results obtained and the general satisfaction given by the method in practice more than compensate for the added time required by the extended primary incubation. Whether or not this long primary period is a *sine qua non* of the method the consensus of experience will determine in time.

Now as to the clinician: Man is a creature of habit and clinicians are no exception to this rule. The habit of many years has accustomed him to the receipt of reports and the completion of the test within a matter of hours and any change from this procedure will, undoubtedly, at first give rise to discussion and even, perhaps, to protest.

It behooves us, therefore, to consider, first, whether or not it is essential for reports to be made within a few hours; and, second, whether in practice this is commonly the case?

In the first place, when considering if it is essential, necessary, or desirable that reports be rendered within a few hours or on the same day that the blood is taken, it is necessary to ascertain the reason for this precipitate haste. It cannot be because of any added danger to the patient by reason of the spread of the infection beyond controllable limits, for if syphilis is to be averted the preventive measures must be initiated within at the most two hours after exposure when neither lesion nor Wassermann reaction are present and, moreover, the treatment of syphilis can never be limited to any definite time regardless of when it is initiated. It cannot be

because the delay, even of days, is unwarrantedly dangerous in the known or suspected syphilitic, for the treatment of the disease is a tedious affair at best and, as a matter of fact, for various reasons, many cases do not report to the doctor again for several days after the blood has been taken, or do not come "until next dispensary or clinic day"—which may be several days off—and, in many others, treatment will not be begun for an appreciable time after the report has been made. Even were the delay deleterious, therefore, as a matter of fact it occurs quite frequently nevertheless. Syphilis is not a disease in which life, death, or ultimate cure is a matter of hours or even days; efficient treatment is a matter of years and while it is true that the earlier treatment is begun, the better the ultimate expectations, a delay of even several days is a matter of little moment in the last analysis. In the early case by the time a positive complement-fixation reaction has appeared the disease has spread beyond local limits; in the late case or one discovered years after insufficient treatment a further delay of a few days before again starting treatment is of little importance.

Secondly, is this matter of rapidity in making and reporting the Wassermann test a fact or merely a fictitious actuality? In this connection the following facts are of interest:

(a) In many laboratories, especially in hospitals, the Wassermann test is made only upon certain days and several days may elapse between the taking of a specimen and the rendering of a report; in fact this is a frequent occurrence and under these circumstances no protest is made by the clinician because these circumstances are a matter of habit and custom.

(b) Many specimens are sent to laboratories by mail and thus varying periods of time are consumed in transit and the examination therefore, delayed. This, again, is a matter to which the clinician is accustomed and so causes no discussion.

(c) At times bloods are held for appreciable periods of time before transmission to the laboratory and, if properly kept, no harm seems to be done by the delay thus occasioned in making the report.

(d) Many patients directed to report to the serologist for the taking of a specimen take their own time for so doing, thus adding days and sometimes weeks to the period elapsing between the requisition, so to speak, and the making of the test.

On analysis, therefore, the matter of a few days more or less between the collection of the specimen and the rendering of a report does not seem to merit the importance given to it at first glance and so does not act as a formidable obstacle in the adoption of a standard technic. In this respect, therefore, the Kolmer modification as described, if it does not actually qualify as a standard method, cannot be said to be disqualified by reason of the extra day required. It is simply a matter of becoming accustomed to the added day.

IV. SPECIFICITY.—This is a very essential requirement of any method and particularly so for a standard technic. It demands: (a) That the reaction, when positive, shall indicate the presence of syphilitic reagin; and (b) that positive reactions shall not occur in the absence of the disease.

The Significance of Positive Reactions with the Kolmer Method. As is well known, the Wassermann test is not a biologically specific reaction and, hence, only relative specificity can be expected and in the past, though non-specific reactions with carefully controlled technics were relatively rare, still they occurred. To the clinician this is a matter of great moment for the making of a false diagnosis based upon a non-specific fixation may be fraught with dire consequences to all concerned.

Certain conditions are well known to give non-specific fixation with syphilitic antigens when tested by methods in ordinary use and it is of interest, therefore, to consider what are the results obtained in them with the Kolmer modification.

1. *Yaws*.—No report has been found in the literature at hand concerning the use of Kolmer's modification in this disease and the condition is not among those included in the present series. It is probable, however, that on account of the similarity between the *Spirocheta pertenuis* and the *Spirocheta pallidum*, the reaction by this or any other method, would be positive. The clinical differentiation of the two diseases, however, does not make this a cause of confusion.

2. *Pneumonia during the Febrile Period*.—In this series there were 8 cases of pneumonia in which the blood was tested during the febrile stage. In 7 of these the Kolmer modification gave a clear-cut negative, one serum giving a 44410 reaction. This case was again tested during convalescence, again gave a positive reaction and a history of infection three years previously was obtained. While this number of cases is too small to warrant any far-reaching conclusions, the results are significant and of some importance and warrant a further study of the blood in pneumonia.

3. *Blood from the Umbilical Cord*.—While notoriously unreliable, these specimens are, nevertheless, frequently taken and often constitute the sole available avenue of investigation, as has been noted elsewhere.⁷ In this series a total of 85 cord bloods were subjected to examination, 81 of which gave negative reactions, there being 4 positives: 44300, 33100, 02210 and 04310. In 3 of these cases a specific history was obtained, infection being denied in the fourth and direct examination of the mother and father being refused. Here, again, the number of specimens examined was too small to permit of final conclusions, but the absence of non-specific fixations and the corroboration of the positives obtained is a remarkable tribute to the specificity of the reactions obtained with this technic.

4. *Leprosy*.—No personal experience has been had with this infection, efforts to obtain leper sera having failed. Kolmer states,⁸

however, that the method has given consistently negative results in a relatively large number of leper sera.

5. *Tuberculosis*.—This is one of the conditions which, at various times, has been said to cause non-specific cross-fixation with syphilitic antigens. The consensus of observation, however, tends to show that this is not the case when a carefully controlled technic is used and the occurrence of a positive syphilitic complement-fixation in a tuberculous serum, therefore, necessitates a careful examination for evidences of syphilis which, however, may not be found clinically and be demonstrable only at autopsy.

In the present series there were 104 cases of tuberculosis in various stages. Of these 10 gave positive reactions with the Kolmer modification. In 2 of these cases a specific history was obtained, one having had a chancre thirty-five years before and giving a 11100 reaction, the other giving a 44440 reaction and admitting a chancre eight years before. A third with a 44444 reaction presented a typical secondary rash clearing up under antiluetic medication; fourth, while denying any history, presented a general adenopathy, and admitted irregular habits. In 4 cases no history was obtained and no definite clinical evidence of syphilis was found, while the remaining 2 cases were lost.

Here, again, the series permits only of generalizations. In view however, of the results obtained with the series as a whole and, also, of the conclusions formulated by other workers with the Wassermann test in tuberculosis, it is quite likely that all of the reactions obtained represented the presence of syphilitic reagin.

Included in the series there were, of course, a large number of varied, non-syphilitic conditions not necessary to tabulate. Of extreme interest and practical value, however, are the facts that, first in no instance where non-specific fixation commonly occurs did fixation occur with the Kolmer modification; and, second, in no instance where fixation occurred and where historical or clinical data were obtainable did these fail to corroborate the results of the test.

It would appear, therefore, that non-specific, false positive reactions are encountered only with extreme rarity with this method, if, indeed, they occur at all.

The combined reports which have so far been published and to which I have had access give a total of 8877 reactions by Kolmer's modification as follows:

Observer.	Number of tests.
Kilduffe ⁹ (previous report, 1014; this report, 1000)	2014
Schamberg and Greenbaum ¹⁰	4000
Shivers ¹¹	320
Harper and Curtis ¹²	120
Palmer and Gibb ¹³	329
Smith ¹⁴	94
Schamberg and Klauder ¹⁵	2000
	<hr/> 8877

In none of these cases were false positives encountered, a fact specially noted by all of these observers. It is safe to say that no other technic in like series and comprising a like variety of conditions has ever given similar results and the results of the combined series tend to indicate that with the Kolmer test non-specific positive reactions do not occur.*

If the cumulative results of other workers substantiate this apparent claim then the method at once establishes a predominant and almost unassailable place in the serological diagnosis of syphilis. To prove or disprove this possibility becomes the duty of all serologists and clinicians interested in syphilis.

In the face of these results the added time necessary to perform the test becomes a matter of extreme insignificance.

Results in Syphilis with Kolmer's Modification. The conclusions drawn from an analysis of the series previously reported¹⁶ are substantiated by the additional experience upon which this report is based and can again be emphasized:

1. A positive reaction obtained with Kolmer's method may be looked upon with a high degree of reliance as indicative of the presence of syphilitic reagin in the blood.

2. A false positive reaction in the absence of syphilitic reagin was not encountered in this series of 2000 cases nor in 8877 cases reported by other observers and is, therefore, an extreme rarity, if, indeed, it occurs at all.

3. The method will detect extremely minute quantities of reagin and, moreover, quantitatively expresses the amount detected.

V. DELICACY. This quality is of vital importance as weighing for or against the adoption of a standard technic for the reasons following:

1. The clinical diagnosis of syphilis is not always an easy nor a simple matter, regardless of the skill of the observer. A standard test, therefore, should be able to detect the disease when clinical signs fail and should be most reliable where skill in diagnosis is at a minimum.

2. The test should be able to detect reagin as early in the infection as possible.

3. Not only gross but minute quantities of reagin should be demonstrable.

4. The reaction should be suitable for the estimation of the efficiency of treatment.

5. False negative reactions should not be obtained with undue frequency.

6. While the occurrence of anticomplementary substances in the serum tested is often due to circumstances beyond the control of the

* At the meeting before which this paper was presented, a number of reports were made by various workers bringing the total number of reactions of Kolmer's technic without demonstrable false positive reactions up to a little over 30,000.

laboratory and the serologist and, at times, of the clinician, such reactions should occur with a minimum of frequency.

In the consideration of the question of delicacy as regards the diagnostic detection of reagin it is, of course, necessary to bear in mind that a certain time must elapse after the appearance of the chancre before reagin appears in the blood in detectable amounts. This time is generally placed at a minimum of twenty-one days—and safely so—and in this connection it is interesting to note that in this series reactions have been obtained as early as three (10,000), four, five, seven, and ten days after the appearance of the initial lesion. While such an early detection of reagin is not to be looked for routinely nor to be diagnostically relied upon, it is a significant tribute to the delicacy of the technic.

The most important conditions formulated by the clinician to be fulfilled by a standard method are that it shall detect reagin with a high degree of accuracy and delicacy and that it will serve as a reliable and efficient control of treatment. The first condition has, to all intents and purposes, been covered in the preceding paragraphs in the consideration of the specificity of the reactions obtained with Kolmer's method. It must be noted here, however, that while a positive reaction can be taken, in view of the evidence at hand, as almost absolute evidence of the presence of reagin in the blood, a like condition does not obtain in the interpretation of the significance of an isolated negative reaction.

In the 2000 cases examined, negative reactions occurred in 14 or 0.7 per cent, in all of which syphilis was undeniably present, some being cases under treatment and giving a positive fixation by another technic.

The occurrence of such false negatives is common to all complement-fixation methods and is illustrative of the vital necessity for repeated serological examinations, not only in the control of treatment, but especially when the test is used as a means of diagnosis. It is essential to remember that the presence of syphilitic reagin is an expression of the interaction of the spirochetæ and the body tissues and its absence at a given time, unless corroborated by repeated observations, is simply an indication of the absence of interreaction between the organisms and the tissues with consequent non-production of reagin or of its production in detectable amounts.

Many authorities have called attention to the fact that syphilitic reagin is not produced in mathematical proportion to the severity of the disease, that it may present a wide range of reactions in known syphilitics without demonstrable cause, and many serologists have noted its selective preference for various antigens.

At the risk of repeating observations made elsewhere¹⁷ as well as the observations of others, it is well again to emphasize the fallacy of relying upon a single negative complement-fixation reaction as conclusive evidence of the absence of syphilitic reagin or

infection. A single negative Wassermann test by any method as yet devised can never be allowed to overshadow the presence of clinical evidences of lues nor can it be made the sole criterion of a sufficiency of treatment. The method may be standardized as to technic but there will always be an unknown quantity impossible to control—the patient. He may be syphilitic and yet, at times, show a marked fluctuation of reagin without demonstrable cause; or it may even be absent, or again, if present, it may fix well with one antigen while reacting indefinitely with another. It would seem trite to emphasize the dubious value of a single negative reaction were it not for the fact that in a surprising number of cases a single Wassermann test is made to take the place of a careful history or even, at times, of anything more than a perfunctory physical examination.

The clinician, therefore, can never place the same degree of reliance in a single negative reaction as can be placed in a positive reaction with Kolmer's method, even though it may be noted that false negative reactions appear to occur with this technic in a minimum of cases.

The Kolmer Method as a Control of Treatment.—It is in the examination of treated cases that this method displays a particular efficiency. A significant feature of the reaction is that it remains positive perceptibly longer than other methods and so leads to more prolonged and, therefore, more efficient treatment before negative reactions can be obtained.

The graphic character of the strictly quantitative readings is of the greatest value as forming a definite index to the degree to which it should be pursued. Of no less importance, as will be noted in a subsequent communication,¹⁸ the readings may be graphically utilized to present to the patient the serological effects of treatment and so encourage him in the persistence necessary to effect a cure; while, for the same reasons, the method is particularly adapted to the study of the efficiency of various therapeutic agents. All observers reporting on the method are unanimous in extolling its efficiency as a control of treatment and none more emphatically than the clinicians.

The occurrence of positive reactions early in the infection is a feature of great practical importance because, as has been noted by Schamberg and Greenbaum,¹⁸ a definite number of primary lesions are negative to dark-field examination as a result of local treatment; and generally negative serologically because the time of the appearance of the reagin in the blood varies with the individual and the sensitiveness of the test employed. The fact that Kolmer's method will not only detect the presence of reagin—but also measure the amount—in as little as 0.0025 cc of serum is a sufficient testimony to its delicacy.

VI. A STANDARD METHOD MUST BE A QUANTITATIVE METHOD.—This has ceased to be a debatable requirement and is conceded by both the clinician and the serologist. Kolmer's method is not only a strictly quantitative method in that it measures the least amount of serum containing reagin, but it also permits of a further refinement in indicating, in terms of $+4$ to $+1$ the amount of reagin present in each serum dilution, thus permitting a distinction between a 44444 and 44321 reaction, although both are "very strongly positive."

VII. DEFINITE READINGS SHOULD BE POSSIBLE IN A HIGH PERCENTAGE OF CASES.—Because of the, at times, unavoidable factors operating to make a serum anticomplementary, such readings will always occur in a varying proportion of cases. With Kolmer's method, however, these are reduced to a minimum, occurring only in 4 cases or 0.2 per cent of 2000 sera in spite of the fact that many were such as would have been—and were—anticomplementary with other methods.

VIII. AGREEMENT WITH CLINICAL FINDINGS.—For the clinician this is almost a *sine qua non* of a standard method. All observers working with Kolmer's method are unanimous in emphasizing the agreement with the clinical findings in a high percentage of cases, an experience borne out in the series herewith reported, so that this requirement is more than fulfilled and in this respect the method qualifies as a standard technic.

Summary.—An analysis is presented of the Kolmer modification of the complement-fixation test in syphilis in a series of 2000 sera in relation to the requirements of the clinician and to those suitable for a standard method. As a result of the data presented, it is concluded that the method is suitable for adoption as a standard test and superior to any as yet proposed for the purpose.

REFERENCES.

1. Kilduffe, R. A.: The Clinical Evaluation of the Wassermann Test, Arch. Dermat. and Syph., 1922, 6, 147.
2. Kilduffe, R. A.: The Status of the Negative Wassermann Reaction, Jour. Am. Med. Assn., 1922, 79, 2215.
3. Kolmer, J. A.: A New Complement-fixation Test for Syphilis Based upon the Results of Studies in the Standardization of Technic, Am. Jour. Syph., 1922, 6, 82.
4. Kolmer, J. A.: Quantitative Complement-fixation Test for Syphilis, Am. Jour. Syph., 1922, 6, 3.
5. Kolmer, J. A.: The Nature of the Complement-fixation Reaction in Syphilis in Relation to the Standardization of Technic, AM. JOUR. MED. SCI., 1923, 165, 612.
6. Kolmer, J. A.: A Superior Antigen for Complement-fixation Tests in Syphilis (a Cholesterolized and Lecithinized Alcoholic Extract of Heart Muscle), Am. Jour. Syph., 1922, 6, 74.
7. Kilduffe, R. A.: The Wassermann Reaction in its Relation to Prenatal and Congenital Syphilis, AM. JOUR. MED. SCI., 1922, 164, 608.
8. Personal communication.
9. Kilduffe, R. A.: The Kolmer Modification of the Wassermann Test; a Report of its Trial in a Series of 1014 Serums, Arch. Dermat. and Syph., 1922, 6, 709.
10. Schamberg, J. F., and Greenbaum, S. S.: Clinical Experience with the Kolmer Complement-fixation Test for Syphilis, Jour. Am. Med. Assn., 1923, 80, 72.

11. Shivers, C. H. D.: Clinical Value of the Kolmer Modification of the Wassermann Test, *Arch. Dermat. and Syph.*, 1922, 6, 334.
12. Harper, J., and Curtis, L. F.: The Kolmer Modification of the Wassermann Test, *U. S. Naval Med. Bull.*, 1922, 17, 757.
13. Palmer, L. J., and Gibb, W. E.: Experience with the Kolmer Quantitative Complement-fixation Test for Syphilis, *Arch. Dermat. and Syph.*, 1922, 6, 739.
14. Smith, F. C.: The Syphilis Complement-fixation Reaction in Pregnancy with Special Reference to the Kolmer Reaction, *Am. Jour. Syph.*, 1922, 6, 705.
15. Schamberg, J. F., and Klauder, J. C.: *Med. Clin. North America*, 1921, 5, 667.
17. Kilduffe, R. A.: The Status of the Negative Wassermann Reaction, *Jour. Am. Med. Assn.*, 1922, 79, 2215.
18. Kilduffe, R. A.: A Graphic Method of Reporting the Wassermann Reaction with a Note upon its Clinical Value, *Jour. Lab. and Clin. Med.*, October, 1923, 9, 1.

THE USE OF INSULIN IN THE MODERN TREATMENT OF DIABETES.*

BY DAVID S. HACHEN, B.S., M.D.;

INSTRUCTOR IN MEDICINE, UNIVERSITY OF CINCINNATI; RESIDENT PHYSICIAN, CINCINNATI GENERAL HOSPITAL.

(From the Medical Clinic, Cincinnati General Hospital, University of Cincinnati.)

INSULIN is the internal secretion of the pancreas. It is the substance which is supplied in insufficient quantities in diabetic individuals. Ever since Langerhans demonstrated the islet tissue in the pancreas and Opie established the hypothesis that diabetes was due to degeneration of this tissue, many investigators have made innumerable, but unsuccessful attempts to extract this substance.

Banting and Best¹ prepared the substance now known as insulin from dog's pancreas removed from seven to ten weeks after ligation of the ducts. Later² they prepared it from the pancreas of the bovine fetus at about the fifth month. Then Collip,³ by means of an elaborate process, prepared insulin used in the first clinical cases, from the whole gland of the adult ox. Extracts prepared by these procedures when injected intravenously and subcutaneously in diabetic animals reduced the percentage of the blood sugar and the daily urinary excretion of sugar. Likewise the blood sugar of normal rabbits could be markedly reduced but when 0.04 per cent was reached convulsions occurred. This finding was made use of in establishing insulin dosage. Thus the term "unit of insulin" was given to that amount which would lower the blood sugar of a starved rabbit to 0.04 per cent, that is, the convulsion point, in from one to four hours. After these facts and others were established, insulin was used on human diabetics with similar results. Banting, Campbell and Fletcher⁴ have recently reported a series of over 50 cases treated

* Read before the Cincinnati Academy of Medicine, May 14, 1923.

with insulin attended with marked clinical improvement, abolition of the glycosuria, maintenance of the blood sugar at the normal level and disappearance of ketones from the urine and blood.

Regardless of the marvelous effect produced by the administration of insulin in human diabetics, great stress must be laid on the dietetic management. Diet still maintains its paramount position in the treatment of diabetes and will therefore be given the first consideration.

In the management of a successful diabetic diet the following points must be considered; (1) the carbohydrate content, (2) the protein content, (3) the fat content and (4) the total caloric content.

The Carbohydrate Content. The efficacy of keeping the carbohydrate content of the diet below the glucose tolerance of the patient is generally conceded. Woodyatt⁵ regards sugar as a stimulant to the sugar-burning mechanism. Thus, the presence of excess of sugar in the metabolic mixture stimulates a diseased pancreas to the point of fatigue and lessened function. Theoretically, then, diminution in the glucose supply should relieve this organ and give it a chance to recuperate. Carbohydrate reduction is always attended with clinical improvement. It seems justified on these grounds, therefore, to keep the carbohydrate content of the diet at a minimum, compatible with the prevention of ketosis.

The Protein Content. A minimum of protein, just sufficient to maintain nitrogen equilibrium, should be used for four reasons: (1) because ingestion of protein throws a large amount of glucose (58 per cent by weight) into the metabolic stream; (2) because the relatively high specific dynamic action of protein produces an undesirable elevation of the basal metabolic rate, as demonstrated by Wilder, Boothby and Beeler;⁶ (3) because the work of Wilder⁷ shows that an excess of protein exerts a specifically depressant effect on the ability of the organism to utilize glucose; and (4) because protein per gram of substance is not as effective in the prevention of ketosis as carbohydrate per gram of substance.

Marsh, Newburgh and Holly⁸ recently published a review of the literature bearing on the minimal protein requirement and concluded that in the diabetic as in the normal, $\frac{2}{3}$ gm. of protein per kilo body weight is sufficient to maintain nitrogen equilibrium, provided the total caloric intake is great enough to supply the metabolic needs of the body. By the use of large quantities of fat they have been able to satisfy the total caloric requirement of the patients and keep them in nitrogen equilibrium on the small quantity of protein allotted.

The Fat Content. The pendulum of fat-feeding is now swinging again in the other direction. The present teaching is that a maximum of fat should be used within the limit of ketosis. This principle of high-fat feeding was considered a very dangerous procedure until Newburgh and Marsh⁹ published their startling results with

diets high in fat. These results were soon explained by some interesting *in vitro* experiments performed by Shaffer,¹⁰ in which he showed that when glucose was added to test tubes containing aceto-acetic acid in the presence of hydrogen peroxide, alkali, proper conditions of temperature, etc., aceto-acetic acid was rapidly oxidized. He found¹¹ that one molecule of glucose accomplished the disappearance of two molecules of aceto-acetic acid when the latter was present in excess. He, therefore, assumed that this "ketolytic" behavior of glucose *in vitro* was evidently analogous to the antiketogenic property of carbohydrate in preventing or abolishing ketonuria in the human subject. He cited numerous cases from the literature in which he calculated the ketogenic anti-ketogenic balance and found that if the total number of ketogenic molecules in the metabolic mixture did not exceed twice the number of ketolytic molecules, ketosis would be at a minimum. This is in keeping with clinical results obtained by Newburgh and Marsh¹² and Wilder and Winter,¹³ although opposed by the views of Woodyatt⁵ and those of Hubbard and Wright.¹⁴ On the basis of a 1 to 1 ratio, *i. e.*, 1 molecule of glucose oxidizing 1 molecule of aceto-acetic acid, Woodyatt has suggested that if the ratio of fatty acid to glucose is greater than 1.5 to 1, acidosis will develop. Newburgh and Marsh¹² in a series of 190 cases produced no acidosis with diets containing a fatty acid to glucose ratio of 2.5 to 3 to 1. Thus it becomes evident that considerable quantities of fat can be used with safety.

The Total Caloric Content. In 1914 Allen introduced the principle of starvation in the treatment of diabetes. It soon became apparent that fasting was not only unpleasant and exhausting, but occasionally caused death. Such a procedure is unnecessary if one analyzes the metabolism during fast.

During fast, an individual does not cease to produce heat. Benedict¹⁵ has shown that on the second day of a fast, a subject produced 1768 calories or 29.9 calories per kilogram and the individual was estimated to have catabolized 74.7 gm. of protein, 147.5 gm. of fat and 23.1 gm. of glycogen. Voit¹⁶ has shown that a well-nourished dog which during starvation burned 96 gm. of body fat, burned 97 gm. when fed 100 gm. of fat. The fat ingested simply burned instead of body fat. Thus if a diabetic during fast reacts essentially as a non-diabetic individual, in the same state of nutrition, and if he weighs 60 kg., produces 1800 calories and in doing so burns 150 gm. of fat, the ingestion of an equal amount of fat should leave his metabolism in the same state as before. If this is true, why then should one ever use complete fasting for diabetics? The method of choice, then, is to feed diets high in fat, containing a sufficient number of calories to satisfy the basal requirement.

From the foregoing, one naturally concludes that the optimal diabetic diet should contain a minimum of carbohydrate, just

sufficient protein to maintain nitrogen equilibrium, the greatest amount of fat possible within the limit of ketosis and sufficient total calories to satisfy the basal requirement.

These requirements are admirably filled in the low-carbohydrate, low-protein, high-fat diets advocated by Newburgh and Marsh.⁹ A list of the diets used are given in Table I showing the total glucose values and fatty acid to glucose ratios.

TABLE I.—NEWBURGH DIETS. HIGH-FAT DIETS SHOWING TOTAL GLUCOSE AND FATTY ACID GLUCOSE RATIOS.

	Protein.	Fat.	Carbo- hydrate.	Calories.	Total glucose.	Ratio FA/G.
No. I . . .	20.51	87.62	14.6	929.0	34.65	2.5
No. II . . .	28.75	138.42	20.31	1442.0	50.8	2.7
No. III . . .	34.31	174.71	29.8	1828.8	67.2	2.5
No. IV . . .	53.62	232.75	36.36	2454.6	90.7	2.6
ADDITIONAL HIGH-FAT DIETS IN USE AT THE GENERAL HOSPITAL.						
1	22.5	113.6	17.6	1182.8	42.0	2.6
2	25.5	125.5	19.1	1307.9	46.4	2.6
3	31.8	157.6	25.3	1646.8	59.5	2.6
4	38.0	183.0	32.0	1927.0	72.0	2.5
5	73.8	201.5	44.5	2273.8	107.5	2.0
6	65.4	241.7	50.4	2638.5	112.1	2.2
7	70.5	247.2	78.1	2819.2	143.7	1.7
8	74.1	248.0	110.2	2969.8	179.0	1.4

Our experience with such a dietary dates from April, 1922. The first case in our series G-1808 a man, aged thirty-seven years, entered the hospital February 27, 1922, complaining of polyuria, polydipsia and polyphagia. The duration of symptoms was one year. He had lost considerable weight, became weak, tired and impotent. Four weeks before entrance there was a general pruritus; one week before entrance edema of feet and ankles developed. On a regular house diet he eliminated 150 to 200 gm. of glucose in the urine with considerable acetone and diacetic acid. The Allen form of treatment was initiated with absolute starvation and the patient became sugar-free on the fifth day. The diet was gradually raised, using equal parts of protein and fat and small quantities of carbohydrate. After six weeks of treatment the diet consisted of 8 gm. of carbohydrate, 49 gm. of protein, 65 gm. of fat, 813 calories and resulted in the appearance of traces of sugar in the twenty-four-hour urinary specimen. In spite of the edema, which persisted, the patient lost 17 pounds in weight, became weaker and weaker until he could hardly stand on his feet. The necessity of increasing the caloric content of the diet became apparent, so, as a last resort, the high-fat diet was given with trepidation. The first diet given consisted

of 14.5 gm. of carbohydrate, 21 gm. of protein, 80 gm. of fat, 858 calories. On this diet he became sugar-free in two days, remained sugar-free for six days. During his remaining five weeks' stay in the hospital, the diet was gradually raised to 2100 calories, using similar proportions of fat, protein and carbohydrate, with the result that the patient's urine remained sugar- and ketone-free; he gained 12 pounds in weight in spite of loss of edema during treatment and left the hospital in excellent condition. Additional data are given in Table II. A subsequent history of this case was fortunately obtained just recently. The patient did splendidly for eight months gaining strength and 10 more pounds in weight. Four months ago he entered a boarding-house where it was considered troublesome to prepare his special diet. He became negligent, ate a regular diet and entered the hospital May 9, in diabetic coma.

TABLE II.—CASE SHOWING TRANSITION FROM ALLEN TO NEWBURGH TREATMENT.

Date, 1922.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Remarks.
				C.	P.	F.	Cal.			
2/28	++++	+++	+++		Incomplete			118	
3/1 to 3/4	150-200	+++	+++		Regular diet					
3/4	99	+++	+++		Starvation			117.5	
3/5	19.2	++++	++		Starvation			.267	114.5	
3/6	15	++++	++		Starvation					
3/7	Trace	++	++		Starvation					
3/8	0	+	○		Starvation			.151	113	
3/9 to 3/19	0	+	○	8.0	16.8	8.0	106	116	Feet edematous.
3/19 to 4/13	0	○	○	5.0	42.5	25.0	415	113	Feet edematous.
4/13 to 4/23	Trace	○	○	8.0	49.0	65.0	813	109	Feet edematous.
4/23 to 4/28	0	○	○	14.5	21.0	80.0	858	101	Feet edematous.
4/28 to 5/28	0	○	○	21.8	33.5	149.8	1504	.15	No edema.
5/28 to 6/4	0	○	○	27.9	42.0	173.0	1824	109	No edema.
6/4	0	○	○	50.2	43.4	191.2	2100	112	No edema.

The favorable result obtained in this case led us to try the high-fat diet in other diabetics. All cases that subsequently entered the hospital were immediately placed on a diet containing 18 to 20 gm. of protein, 12 to 15 gm. of carbohydrate, 85 to 90 gm. of fat, equivalent to 800 to 1000 calories. The patients remained on this diet until sugar-free for four to six days; the diets were then gradually increased until a maximum diet was reached which was within the patient's tolerance. In all, 52 cases have been treated in this fashion. Seventeen cases are presented in Table III to show the results obtained. On the initial diet, patients became sugar-free in from two to fourteen days; ketosis disappeared two to four

TABLE III

Case.	Sex.	Age at admission.	Probable duration of diabetes.	Body weight pounds.		Final.	Complications.	Initial diet, grams.				Urine.		Blood sugar, per cent.		Final diet, grams.			
				Before diabetes.	At admission.			C.	P.	F.	Cal.	Day sugar-free.	Day acetone-free.	On admission.	On discharge.	C.	P.	F.	Cal.
G-1808	M.	37	1 yr.	107	112	None	15.0	21.0	80.0	864	0	0	.267	.15	50.0	43	191	2091
G-5402	M.	49	3 mos.	145	111	108	None	15.0	21.0	87.0	927	11	12	.228	.14	36.0	53	233	2453
G-4982	F.	54	5 yrs.	185	130	125	None	22.0	22.0	90.0	986	14	18	.75	.18	31.0	29	143	1527
G-5294	M.	41	10 yrs.	230	195	190	Furuncles	15.0	21.0	80.0	864	7	14	.589	.295	28.0	36	147	1579
G-3514	F.	56	1 yr.	200	123	122	None	14.5	21.4	80.3	858	3	6	.33	.22	32.9	53	215	2285
G-5273	M.	27	1 yr.	147	147	None	22.0	22.0	90.0	986	3	0	.222	.08	41.0	58	273	2847
G-6181	M.	55	?	128	126	Infection	15.0	21.0	80.0	864	4	0	.18	36.0	53	233	2453
G-7331	M.	42	11 yrs.	230	192½	187	Furuncles	15.0	21.0	80.0	864	3	6	.4	.105	36.0	53	233	2453
G-5530	M.	44	4 yrs.	190	123½	117	None	14.6	20.5	87.6	929	6	14	.25	.16	40.0	60	244	2596
H-534	F.	49	2 yrs.	135	134	None	15.0	21.0	80.0	864	5	11	.35	.12	46.0	89	313	3357
H-1194	F.	49	6 mos.	None	12.0	27.0	92.0	984	4	10	.258	.13	36.0	53	233	2453
H-3103	F.	61	10 yrs.	211	146	144	Beginning gangrene	20.0	22.0	91.0	987	2	9103	30.0	34	174	1822
H-3025	F.	58	11 yrs.	186	126	125	None	15.0	21.0	82.0	882	3	2	.36	.18	30.0	34	176	1840
H-2976	F.	52	1 yr.	203	140	134½	Gangrene	20.0	22.5	91.0	989	4	0	.25	.167	36.0	54	237	2493
H-2977	F.	42	2 yrs.	230	184	178	None	20.0	23.0	91.0	991	4	14	.155	.114	36.0	54	237	2493
H-3107	M.	39	2 mos.	160	137½	134	None	15.0	21.0	80.0	864	4	9	.137	.09	36.0	54	232	2448
H-2723	F.	56	2 yrs.	200	118½	117	Gangrene	15.0	21.0	87.0	927	16	16	.223	.14	30.0	34	175	1831

days after freedom from glycosuria; the blood sugar dropped to normal level and there was definite clinical improvement. This list includes only cases admitted on the medical service who were known to follow the diet. It does not include cases of diabetic coma, nor are cases included which did not obey instructions during observation. In 2 cases a maximum diet of only 1500 calories could be given. The remainder of the cases were discharged upon diets containing over 1800 calories, the majority of these in the vicinity of 2400 calories.

Case Reports. Detailed reports of 5 cases are given to show the effects of the high-fat diet.

CASE I.—M. D., H-1194, female, aged forty-nine years, entered the hospital February 26, 1923, complaining of abdominal trouble. She was not aware that she had diabetes, which was discovered during the routine examination. This patient was placed on a diet containing 12.3 gm. of carbohydrate, 27.2 gm. of protein, 92.7 gm. of fat, 994 calories, and became sugar-free in two days. Patient remained sugar-free as diet was gradually increased to 2456 calories with a fat content of 232.7 gm. The blood sugar dropped from .258 to .147 per cent. For further details see Table IV.

TABLE IV.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Total, G.	Ratio FA/G.	Blood sugar, per cent.	Weight in pounds.
				C.	P.	F.	Cal.				
2/26	65.8	+	○								
2/27	2.37	○	○	12.3	27.2	92.7	994	37	2.6		
2/28	0	Trace	○	14.6	24.7	94.0	1003	38	2.5	.258	
3/1	0	Trace	○	20.3	22.6	90.4	988	42	2.1	169
3/2	0	○	○	14.8	25.3	86.2	935	38	2.3		
3/3	0	○	○	15.3	22.6	96.6	1021	38	2.5		
3/4	0	○	○	20.3	28.7	138.4	1423	51	2.7		
3/5	0	○	○	20.3	28.7	138.4	1423	51	2.7	171
3/6	0	○	○	20.3	28.7	138.4	1423	51	2.7		
3/7	0	○	○	20.3	28.7	138.4	1423	51	2.7		
3/8	0	○	○	29.8	34.3	174.7	1826	67	2.6		
3/9	0	○	○	29.8	34.3	174.7	1826	67	2.6		
3/10	0	○	○	29.8	34.3	174.7	1826	67	2.6	169
3/11	0	○	○	36.3	53.6	232.7	2456	90	2.5		
3/12	0	○	○	36.3	53.6	232.7	2456	90	2.5		
3/13	0	○	○	36.3	53.6	232.7	2456	90	2.5	.147	
3/14	0	○	○	36.3	53.6	232.7	2456	90	2.5	170
3/15	0	○	○	36.3	53.6	232.7	2456	90	2.5		

CASE II.—S. D., G-4982, female, aged fifty-four years, entered the hospital August 15, 1922, complaining of painful and swollen feet. Sugar was found in her urine five years previously; she had lost 50 pounds in weight. Considerable sugar, acetone and diacetic acid were found in the urine. Blood sugar was 0.75 per cent, alkali reserve 44. On a diet containing 22.3 gm. carbohydrate, 22.3 gm. protein, 90.3 gm. fat, 991 calories, the patient became sugar-free in

fourteen days. The diet was raised to 1526 calories which seemed to be all that she could tolerate. See Table V.

TABLE V.

Date.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Total G.	Ratio FA/G.	Blood sugar, per cent.
				C.	P.	F.	Cal.			
7/16/22	++++	+++	Incomplete						
7/17/22	25.0	++++	++++	Regular diet				2007		
7/18/22	165.0	++++	++++	Regular diet				2007		
7/19/22	56.0	++++	++++	22.3	22.3	90.3	991	44.2	2.0	.75
7/20/22	21.4	++++	++++	22.3	22.3	90.3	991	44.2	2.0	
7/21/22	11.3	++++	++++	22.3	22.3	90.3	991	44.2	2.0	
7/22/22	13.8	+++	++	22.3	22.3	90.3	991	44.2	2.0	
7/23/22	19.5	++	+	22.3	22.3	90.3	991	44.2	2.0	
7/24/22	7.0	+	+	22.3	22.3	90.3	991	44.2	2.0	
7/25/22	6.5	Trace	Trace	22.3	22.3	90.3	991	44.2	2.0	
7/26/22	4.0	Trace	Trace	22.3	22.3	90.3	991	44.2	2.0	
7/27/22	14.9	Trace	○	22.3	22.3	90.3	991	44.2	2.0	
7/28/22	2.1	○	○	22.3	22.3	90.3	991	44.2	2.0	
7/29/22	6.5	○	○	22.3	22.3	90.3	991	44.2	2.0	.18
7/30/22	Trace	○	○	22.3	22.3	90.3	991	44.2	2.0	
7/31/22	Trace	○	○	22.3	22.3	90.3	991	44.2	2.0	
8/1/22	2.0	○	○	22.3	22.3	90.3	991	44.2	2.0	
8/2/22	0	○	○	22.3	22.3	90.3	991	44.2	2.0	
8/3/22	0	○	○	22.3	22.3	90.3	991	44.2	2.0	
8/4/22	0	○	○	30.6	29.4	142.9	1526	61.9	2.2	
8/5/22	0	○	○	30.6	29.4	142.9	1526	61.9	2.2	
8/6/22	0	○	○	30.6	29.4	142.9	1526	61.9	2.2	
8/7/22	0	○	○	30.6	29.4	142.9	1526	61.9	2.2	

CASE III.—J. W., G-5530, male, aged forty-four years, who had had diabetes for four and a half years, entered the hospital complaining of thirst, polyuria, polyphagia, weakness and numbness of extremities. Former weight 190 pounds; present weight 125 pounds. Considerable glucose, acetone and diacetic acid were found in the urine. On a diet containing 14.6 gm. of carbohydrate, 20.5 gm. of protein, 87.6 gm. of fat and 929 calories, the patient became sugar-free on the sixth day. The acetone and diacetic acid disappeared a day later. He responded nicely to the usual dietary increases until a dose of neosalvarsan was given for his lues. The following day sugar, acetone and diacetic acid appeared in the urine. The diet was again decreased, but it was not until the second day of a starvation diet that the patient became sugar-free, on the eighteenth day after the reappearance of sugar in the urine. Following this incident the patient made an uneventful partial recovery. See Table VI.

CASE IV.—W. R., G-5402, male, aged forty-nine years, entered the hospital complaining of the usual diabetic symptoms of three months' duration. During the past four weeks he had lost 34 pounds in weight. On a diet similar to the one stated in the preceding case, the patient became sugar-free on the eleventh day. Acetone and diacetic reactions of the urine were negative about a week later. This patient responded nicely to dietary increases up to 2456 calories. The blood sugar dropped from 0.228 per cent to 0.144 per cent. See Table VII.

TABLE VI.—CASE SHOWING EFFECT OF NEOSALVARSAN ON CARBOHYDRATE TOLERANCE.

Date, 1922.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds	Remarks.
				C.	P.	F.	Cal.			
8/10	44.6	+++	+++	14.6	20.5	87.6	929	123½	
8/11	40.9	+++	++	14.6	20.5	87.6	929	.222		
8/12	23.3	++	++	14.6	20.5	87.6	929			
8/13	13.0	+	+	14.6	20.5	87.6	929			
8/14	4.3	++	+	14.6	20.5	87.6	929			
8/15 to 8/18	0	+	+	14.6	20.5	87.6	929			
8/18 to 8/21	0	○	○	27.8	29.7	141.2	1415	.230		
8/21 to 8/23	0	○	○	26.2	34.2	176.0	1827			
8/23	0	○	○	26.2	34.2	176.0	1827	.2559 neosalvarsan given.
8/24	15.4	+	+	26.2	34.2	176.0	1827	Arm painful and swollen.
8/25	13.4	+	+	26.2	34.2	176.0	1827	Arm painful and swollen.
8/26 to 8/31	15 to 22	+	+	20.3	28.7	138.0	1438	Arm painful and swollen.
8/31 to 9/9	10 to 15	+	+	14.6	20.5	87.6	929	Arm painful and swollen.
9/9	+++	+	+		Starvation			Arm improved
9/10	++	++	++		Starvation					
9/11	0	++	++		Starvation					
9/12 to 9/16	0	○	○	14.6	20.5	87.6	929			
9/16 to 9/19	0	○	○	20.3	28.7	138.0	1438			
9/19 to 9/22	0	○	○	26.3	34.2	176.0	1827			
9/22 to 9/25	0	○	○	36.3	53.6	232.7	2456	.169		

TABLE VII.

Date.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Total G.	Ratio FA/G.	Blood sugar, per cent.	Weight of patient, lbs.
				C.	P.	F.	Cal.				
8/3/22	45.6	++++	++++		Incomplete						
8/4/22	12.6	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5	.228	
8/5/22	65.1	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5		
8/6/22	21.4	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5		
8/7/22	22.8	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5		
8/8/22	14.8	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5	110
8/9/22	10.6	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5		
8/10/22	21.8	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5	110
8/11/22	13.9	++++	++++	14.6	20.5	87.6	929.0	35.3	2.5		
8/12/22	13.4	++	++	14.6	20.5	87.6	929.0	35.3	2.5		
8/13/22	7.0	++	+	14.6	20.5	87.6	929.0	35.3	2.5		
8/14/22	0	+	—	14.6	20.5	87.6	929.0	35.3	2.5		
8/15/22	0	—	—	14.6	20.5	87.6	929.0	35.3	2.5	110
8/16/22	0	—	—	14.6	20.5	87.6	929.0	35.3	2.5	109½
8/17/22	0	—	—	27.8	29.7	141.2	1415.0	59.1	2.3	109
8/18/22	0	+	+	27.8	29.7	141.2	1415.0	59.1	2.3	108
8/19/22	0	+	+	27.8	29.7	141.2	1415.0	59.1	2.3		
8/20/22	0	—	—	26.2	34.2	176.2	1827.7	63.6	2.7		
8/21/22	0	Trace	Trace	26.2	34.2	176.2	1827.7	63.6	2.7	108
8/22/22	0	—	—	26.2	34.2	176.2	1827.7	63.6	2.7		
8/23/22	0	—	—	26.2	34.2	176.2	1827.7	63.6	2.7	.144	108
8/24/22	0	—	—	26.2	34.2	176.2	1827.7	63.6	2.7		
8/25/22	0	—	—	26.2	34.2	176.2	1827.7	63.6	2.7		
8/26/22	0	—	—	36.3	53.6	232.7	2456.0	90.6	2.5	107
8/27/22	0	—	—	36.3	53.6	232.7	2456.0	90.6	2.5	106½
8/28/22	0	—	—	36.3	53.6	232.7	2456.0	90.6	2.5	107½
8/29/22	0	—	—	36.3	53.6	232.7	2456.0	90.6	2.5	107½
8/30/22	0	—	—	36.3	53.6	232.7	2456.0	90.6	2.5	107½

CASE V.—L. E., H-2976, female, aged fifty-two years, entered the hospital complaining of diabetes, complicated by gangrene of the left great toe. The duration of diabetes was not known. She had lost 50 pounds in weight during the past two years. After receiving the 929 calories diet she became sugar-free on the fourth day. The gangrenous toe was amputated May 12, 1923. Remainder of patient's stay in hospital was uneventful. See Table VIII.

TABLE VIII.—CASE WITH GANGRENE OF GREAT TOE; IMPROVED UNDER TREATMENT. AMPUTATION.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds
				C.	P.	F.	Cal.		
4/21	32.8	—	—	14.6	20.5	87.62	929.0	139½
4/22	14.49	—	—	14.6	20.5	87.62	929.0		
4/23	12.0	—	—	14.6	20.5	87.62	929.0		
4/24	—	—	—	14.6	20.5	87.62	929.0		
4/25	—	—	—	22.6	20.3	90.8	988.8	.25	139½
4/26	—	—	—	22.6	20.3	90.8	988.8		
4/27	—	—	—	27.82	29.70	141.27	1415.7		
4/28	—	—	—	27.82	29.70	141.27	1415.7		
4/29	—	—	—	27.82	29.70	141.27	1415.7		
4/30	—	—	—	27.82	29.70	141.27	1415.7		
5/1	—	—	—	27.82	29.70	141.27	1415.7		
5/2	—	—	—	27.82	29.70	141.27	1415.7		
5/3	—	—	—	27.82	29.70	141.27	1415.7		
5/4	—	—	—	26.24	34.22	176.21	1827.7		
5/5	—	—	—	26.24	34.22	176.21	1827.7		
5/6	—	—	—	26.24	34.22	176.21	1827.7	134½
5/7	—	—	—	26.24	34.22	176.21	1827.7		
5/8	—	—	—	25.03	34.78	167.10	1706.2	.167	
5/9	—	—	—	36.36	53.62	232.75	2456.6		
5/9 to 6/9	—	—	—	36.36	53.62	232.75	2456.6	.146	

Thus the remarkable improvement noticed under this form of treatment has never caused us to regret the change from the former starvation, severe undernutrition style of treatment to the present high-fat feeding.

When insulin became available the treatment was modified as follows: Comatose and precomatose patients received insulin immediately. The others were placed on diets which were 20 per cent over the basal requirement. This included 10 per cent for the specific dynamic action of food and 10 per cent for slight activity in bed. For clinical purposes about 30 calories per kilo sufficed. For example, a patient weighing 50 kilos would receive a diet containing 1500 calories. The high-fat diets described above were used. Patients remained in bed on this diet for a week while daily blood and urine examinations were made. Those who became sugar-free were advised to continue the dietetic treatment. The others were given insulin. To obtain the maximum effect from insulin at the time when food absorption was at its height, the doses were given fifteen to thirty minutes before a meal. Subcutaneous adminis-

tration was the method of choice. During the experimental stages of investigation small doses of insulin were given twice daily, before breakfast and supper, and the effect upon the blood sugar was determined. By noticing the amount of additional glucose utilized by the administration of definite quantities of insulin, it soon became apparent that one unit of insulin provided for the utilization of approximately 2 gm. of glucose. In subsequent cases the dosage of insulin was regulated accordingly, so that after a week's observation the amount of insulin required in a given case could be predicted with some accuracy.

There is a direct relationship between the amount of insulin given and the quantity of glucose utilized. Thus it is advantageous to construct a diet which contains a maximum number of calories with a minimal amount of available glucose. If the high-fat diet used in these experiments is carefully analyzed, one observes that there are 28 calories present in the diet for each gram of available glucose. A diet of 1700 calories, for example, contains 60 grams of available glucose. Comparing this with an ordinary Allen diet of the same caloric value containing 100 gm. each of protein, fat and carbohydrate one finds a total glucose content of 168 grams or 10 calories for each gram of glucose. A total diabetic placed on each of these diets would require 30 units of insulin on the former, 84 units on the latter, a difference of 54 units. The optimal diet, then, becomes economical for two reasons. In the first place, it enables the ordinary case of diabetes with a fair glucose tolerance to handle a diet sufficient in number of calories and compatible with earning a livelihood in which the amount of activity required is not excessive. In the second place, if the patient's glucose tolerance is not sufficient to maintain him on an adequate diet, fewer number of insulin units will be required with less financial strain on the patient.

During the last three to four days of the preliminary observation the morning blood sugar reaches a fairly constant level and the amount of glucose excreted in twenty-four hours is also fairly constant. This amount of glucose, divided by 2, represents the number of insulin units administered in twenty-four hours. If small quantities of glucose, 2 to 5 grams are still eliminated during the twenty-four-hour period, the following method of procedure is used: Two-hourly urine examinations for sugar are made to determine at which time during the day glucose is escaping. The dose of insulin is either increased or properly timed to eliminate this period of glycosuria. Attempts are made to keep the urine sugar-free and the blood sugar at the normal level. Five to 7 additional units of insulin are usually required to bring the blood sugar down to the normal level after the urine is sugar-free.

Results. Up to the present time 15 cases have been treated with insulin. The most striking results have been obtained in children,

young adults and uncomplicated cases of coma. During insulin treatment the first signs of improvement noted are symptomatic. One patient stated that he had a feeling of well-being after each injection. If proper doses of insulin are given, the urine becomes sugar-free, the blood sugar drops to the normal level, ketones disappear from the urine and the patients improve clinically. If the diet given is over the basal calorie requirement, the patients gain rapidly in weight. One patient who had lost 10 pounds in weight during several months regained the weight lost in a week's time. The average severe case of diabetes requires about 20 to 30 units of insulin daily to keep him sugar-free on a diet containing 2400 calories.

The following case illustrates some of the points discussed:

A. E., H-2975, male, aged sixty years, while attempting to pass an insurance examination seven years ago, was told that he had diabetes. During the past two years he had been suffering from excessive thirst, polyuria and loss of weight (30 pounds during past year). On entrance into hospital considerable sugar, acetone and diacetic acid were found in the urine. On a diet containing 20 gm. of carbohydrate, 28 gm. of protein, 140 gm. of fat, 1452 calories, the patient eliminated from 10 to 18 gm. of glucose during twenty-four hours. The diet was increased to 1652 calories, thus increasing the total glucose by 10 gm. and 10 units of insulin were given subcutaneously in one dose before breakfast. On the third day the patient became sugar-free; the acetone and diacetic acid disappeared five days later. The diet was increased first to 1825 calories and then to 2453 calories. The patient remained sugar-free. Blood sugar 0.18 on admission dropped to 0.105 and then rose to 0.15 just before discharge. See Table IX.

TABLE IX.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diacetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.
				C.	P.	F.	Cal.			
4/22	+++	+++	+++		Incomplete			.18	109	
4/23	18.0	+++	+++	20.0	28.0	140	1452	109	
4/24	13.4	+++	+++	20.0	28.0	140	1452	109	
4/25	10.0	++	++	20.0	28.0	140	1452	109	
4/26	18.5	++	++	20.0	28.0	140	1452	108	
4/27	15.4	++	++	23.0	39.0	156	105	
4/28	9.6	+	+	23.0	39.0	156	1652	105	10
4/29	5.4	+	+	23.0	39.0	156	1652	106	10
4/30	0	+	+	23.0	39.0	156	1652	106	10
5/1	0	+	+	23.0	39.0	156	1652	107	10
5/2	0	+	+	23.0	39.0	156	1652	106	10
5/3	0	+	+	23.0	39.0	156	1652	105	10
5/4	0	-	-	26.2	34.2	176	1825	105	10
5/5	0	-	-	26.2	34.2	176	1825	105	10
5/6	0	-	-	26.2	34.2	176	1825	106	10
5/7	0	-	-	26.2	34.2	176	1825	.105	106	10
5/8	0	-	-	36.0	53.0	233	2453	106	10
5/9	0	-	-	36.0	53.0	233	2453	106	10
5/10	0	-	-	36.0	53.0	233	2453	.15	106	10

TABLE X.

Date, 1922-23.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.	Remarks.
				C.	P.	F.	Cal.				
11/22 to 12/1	30-36	+++	+++	14.4	21.6	82.4	850	.258	91	0	
12/1 to 12/12	35-45	+++	+++	34.3	60.0	166.0	1879	.266	101	0	
12/12	9.1	+++	+++	34.3	60.0	166.0	1879	101	80	
12/13	0	++	++	34.3	60.0	166.0	1879	102	120	
12/14	0	++	++	34.3	60.0	166.0	1879	.085	102	80	
12/15	12.4	++	++	34.3	60.0	166.0	1879	102	0	
12/16 to 12/20	25-38	+++	+++	34.3	60.0	166.0	1897	102	0	
12/20	31.7	+++	+++	34.3	60.0	166.0	1879	102	325	By mouth
12/21 to 12/30	20-25	+++	+++	34.3	60.0	166.0	1879	.289	100	50	
12/30	44.0	+++	+++	34.3	60.0	166.0	1879	99	100	By rectum
12/30 to 1/8	18-25	+++	+	34.3	60.0	166.0	1879	95	50	
1/8	15.0	+++	-	34.3	60.0	166.0	1879	95	50	
1/9	17.7	++	-	34.3	60.0	166.0	1879	95	50	
1/10	3.2	++	-	34.3	60.0	166.0	1879	95	50	
1/11	0	++	-	34.3	60.0	166.0	1879	95	50	
1/12	0	++	-	34.3	60.0	166.0	1879	95	60	
1/13	0	++	-	34.3	60.0	166.0	1879	95	50	
1/14 to 1/16	0	+	-	34.3	60.0	166.0	1879	95	40	
1/16	0	+	-	34.3	60.0	166.0	1879	95½	30	
1/17 to 1/20	0	+	-	34.3	60.0	166.0	1879	.24	96	20	
1/20	0	+	-	34.3	60.0	166.0	1879	96	10	
1/21	Trace	++	-	34.3	60.0	166.0	1879	96	10	
1/22	2.19	++	-	34.3	60.0	166.0	1879	96	20	
1/23	0	○	-	34.3	60.0	166.0	1879	96	0	
1/24 to 1/28	Trace	+	-	34.3	60.0	166.0	1879	96	0	
1/28 to 2/10	2.3-20	+	-	34.3	60.0	166.0	1879	96	0	Insulin by mouth.

TABLE XI.

Date, 1923.	Sugar in urine, gm.	Acetone.	Diabetic acid.	Diet in grams.				Blood sugar, per cent.	Weight in pounds.	Insulin units.
				C.	P.	F.	Cal.			
4/14	41.0	+++	++	38	48.5	129	1507	.37	104	20
4/15	25.2	+++	++	38	48.5	129	1507	105	20
4/16	55.0	+++	++	38	48.5	129	1507	30
4/17	22.8	+++	++	38	48.5	129	1507	106	30
4/18	24.0	++	+	38	48.5	129	1507	107	30
4/19	22.8	++	+	38	48.5	129	1507	110	50
4/20	16.2	++	+	38	48.5	129	1507	111	50
4/21	12.0	++	+	38	48.5	129	1507	112	50
4/22	8.0	++	+	38	48.5	129	1507	113	50
4/23	6.9	++	+	38	48.5	129	1507	114	50
4/25	0	+	+	38	48.5	129	1507	114	50
4/26	0	Trace	+	38	48.5	129	1507	114	50
4/27	0	Trace	+	38	48.5	129	1507	.20	114	35
4/28	0	○	○	50	60.0	175	2015	114	35
4/29	0	○	○	50	60.0	175	2015	113	35
4/30	0	○	○	50	60.0	175	2015	113	35
5/1	0	○	○	50	60.0	175	2015	113	35
5/2	0	○	○	50	60.0	175	2015	113	35
5/3	0	○	○	50	60.0	175	2015	113	35
5/4	0	○	○	50	60.0	175	2015	113	35
5/5	0	○	○	50	60.0	175	2015	114	30
5/6	0	○	○	50	60.0	175	2015	114	30
5/7	0	○	○	50	60.0	175	2015	114	30
5/8	0	○	○	50	60.0	175	2015	.167	114	30
5/9	0	○	○	50	60.0	175	2015	114	30
								114	30

The Glucose Tolerance. In all of our cases during the short period of observation there was a noticeable increase in the glucose tolerance as evidenced by the decrease in insulin necessary to maintain patients aglycosuric. In 1 case the dose was decreased from 120 units per day to 20 units per day on an 1800 caloric diet (Table X). In another case the dosage was decreased from 50 to 20 units on the same diet (Table XI). In 2 cases sufficient tolerance was regained so that insulin was discontinued and the patient discharged on an adequate diet.

Treatment of Coma Cases. No definite plan of treatment of coma is as yet available. Banting, Campbell and Fletcher⁴ in a recent communication were not prepared to lay down definite rules for the management of diabetics in coma.

The plan of treatment in vogue at the Cincinnati General Hospital is briefly as follows: Patients brought into the hospital in coma are covered with warm blankets and surrounded by hot-water bottles. Blood is taken for examination and 50 units of insulin administered intravenously in 200 cc of 15 per cent glucose. Blood is examined for sugar and alkali reserve before and several hours after injection of insulin. Usually in three to four hours clinical improvement is noted, sometimes to the point of returning consciousness. Large doses of insulin are continued hypodermatically together with glucose intravenously or by mouth; the latter method is the one of choice, if the patient is conscious. Inasmuch as the coma is due to the products of disturbed fat metabolism, the foremost concern in the early treatment is the prevention of accumulation of these products. Large quantities of glucose are given with large doses of insulin to create a tremendous metabolic fire, so that the further accumulation of ketone bodies ceases. The ketone bodies already present are washed out with large quantities of fluid and alkali. Fluids are given by every avenue of approach and patients in their desiccated state will take up 5000 to 6000 cc in twenty-four hours. Alkalies are given in the form of sodium bicarbonate per rectum or intravenously. As soon as the patient emerges from coma, measured quantities of food are given with insulin. The amounts of insulin required at this stage are larger than ordinarily required; perhaps one or more units per gram of glucose. In the uncomplicated cases of coma the results obtained are miraculous. Within three to four hours the patient begins to respond to painful stimuli. Soon after, the blood alkali reserve commences to rise. In a short time the ketone bodies disappear from the urine and the blood sugar falls. At this stage the treatment must be accurately checked up by laboratory data. Fall in the blood sugar and absence of glycosuria are indications for the administration of more glucose. Failure of a rise in the alkali reserve is indication that more insulin is required.

Five cases of coma have been treated at the Cincinnati General Hospital, death occurring in three. In each of these 3 cases, at the time of death, the blood sugar was normal or only slightly above the normal and the urine was sugar-free. One case died of uremia, 1 died of a multiplicity of complications, and 1 case entered the house in coma on two occasions, each time was resuscitated and finally died a month after the second admission with bronchopneumonia. Necropsies were obtained in all the cases. In the 2 remaining cases, without complications, the recovery was easy and uneventful.

One case, a man, aged thirty-eight years, entered the hospital at 4 P.M. May 9, 1923, complaining of general weakness and shortness of breath. Breathing was Kussmaul in type. There was a cherry-red cyanosis to lips and nail beds. At 7 P.M., three hours later, the patient was in a semistuporous condition. The reflexes were absent. He did not respond to the prick of a pin. There was a marked general desiccation. Pulse was rapid, thumping, irregular in rhythm. Respiratory rate was 30. Extreme air-hunger was present. A sickening fruity odor of breath was present; 1025 cc of urine passed on entrance, contained 51 gm. of glucose, some albumin, considerable quantities of acetone and diacetic acid. Blood sugar was 0.625, alkali reserve 26. Swallowing reflex was fortunately still present, so that fluids could be forced by mouth. During preinsulin days, such a case never recovered.

Treatment. Fifty units of insulin were given hypodermatically at 8 P.M., followed by 100 cc of 5 per cent glucose solution every half hour for four hours and then every hour for the next twenty hours. Five grams of sodium bicarbonate dissolved in 120 cc of water was forced hourly for twenty-four hours. Fifty units of insulin was again given at midnight. During the first twenty-four hours the patient received 100 units of insulin, 140 gm. of glucose, 120 gm. of sodium bicarbonate and 5000 cc of fluid.

The following morning, the blood sugar was 0.215; alkali reserve was 50. The patient was conscious, Kussmaul breathing had disappeared and the general appearance was greatly improved. Considerable quantities of glucose were present in the urine but no diacetic acid was found. Thirty-six hours after admission the patient was sitting up in bed reading a newspaper. An 1800 caloric diet was then started with 20 units of insulin per day. The patient is now doing nicely. This patient is the individual mentioned earlier in this report who was the first case placed on the high-fat régime. His previous tolerance before leaving the hospital was established at 2200 calories with a total glucose content of 78. We will have occasion to study this case again and determine the effect of the precipitation of coma due to dietary excess on the glucose tolerance. See Table XII.

TABLE XII.—CASE OF DIABETIC COMA.

Date, 1923.	Time.	Sugar in urine.	Acetone.	Diacetic acid.	Blood sugar.	Alk. reserve.	Diet.	Insulin units.	Remarks.
5/9	8 P.M.	++++	++++	++++	.65	26	5 per cent glucose	50	Dyspnea, stupor cherry-red cyanosis, lessened sensibilities, diminished reflexes.
	12 M.	5 per cent glucose	50	Less dyspnea.
5/10	8 A.M.	++++	++	—	.215	50	5 per cent glucose	0	Marked improvement.
5/11	8 A.M.	++++	+	—	.265	52	1826 calories high-fat	20	Bright and cheery, reading newspaper.
5/12	8 A.M.	○	—	—	Same diet	20	Feeling well.
5/13	8 A.M.	○○	—	—	Same diet	20	Feeling well.
5/14	8 A.M.	+++	+	—	Same diet	20	Feeling well.
5/15	8 A.M.	—	—	—	Same diet	20	Up and about.
5/16	8 A.M.	○○○	—	—	Same diet	20	Up and about.
5/17	8 A.M.	○	—	—	.243	..	Same diet	20	Up and about.

Hypoglycemic Reactions. In the treatment of cases of diabetes with insulin an occasional reaction may follow a fall in the blood sugar to below the normal level (hypoglycemia). According to Banting, the occurrence of this reaction depends on the rapidity of the fall as well as the per cent of the blood sugar. This may happen in spite of the extreme care exerted in controlling insulin administration by careful laboratory work. In a large diabetic clinic such reactions occur frequently. Campbell, at the recent meeting of the Society for Clinical Investigation at Atlantic City, reported as follows: When the blood sugar falls to 0.08 to 0.07 per cent there is a feeling of nervousness or uneasiness; patients complain of hunger and weakness; at 0.07 to 0.05 per cent there is always a profuse sweat; between 0.05 and 0.04 per cent there is delirium, excitement, sensory and motor aphasia, delusions, dysarthria and a bradycardia; at 0.035 per cent there is unconsciousness, lost or increased reflexes, increased muscle tonus, tremor. In our series we can only report a single occurrence of a hypoglycemic reaction.

A woman, aged fifty-five years, entered the hospital for the second time in diabetic coma. She was resuscitated by the treatment described above and finally placed on a diet controlled by 45 units of insulin per day. On the day that the reaction occurred the patient failed to eat the entire quantity of food given. The patient was constantly complaining of a cold feeling in her neck, headache and a burning sensation in the stomach. At 7 P.M., she suddenly appeared very stuporous. She was lying on her side, eyes wide open, facial expression blank. When asked questions, she mumbled unintelligibly. She failed to recognize her husband who was sitting

at the bedside. Respirations were quiet, deep and regular. Pulse was slow, good volume and tension, rhythm regular. Blood-pressure was systolic 140, diastolic 80. Body was flaccid. Pupils were equal, normal size, reacted to light. The left face twitched. At 8 P.M. coma had deepened. The arms and legs began to twitch. Right arm was moderately spastic. Knee-jerks were equal but sluggish. Biceps- and radial-jerks were equal and active. Plantar signs were normal. Pupils equal and reacted to light. Patient did not respond to painful stimuli. During examination there were rhythmical contractions of the diaphragm simulating attempts to retch. The blood sugar was 0.032 per cent, alkali reserve 73.

At 8.25 P.M. injection of 15 per cent glucose was begun intravenously. Within two minutes the patient opened her eyes and recognized her husband. Five minutes later there was a violent reaction; patient screamed, cried and struggled fiercely. The remainder of glucose was given with some difficulty, two persons being required to restrain patient. Morphine sulphate, gr. $\frac{1}{6}$, was given hypodermically. Patient gradually quieted down during the next ten minutes. Blood sugar fifteen minutes after glucose administration was 0.276 per cent, alkali reserve 70. The following day the patient was very comfortable. The blood sugar was 0.25 per cent, alkali reserve 64.

These hypoglycemic reactions can be easily relieved by administration of 10 to 20 gm. of glucose in a glass of orangeade.

Recovery is immediate. When the patient is unconscious 1 cc of adrenalin (1 to 1000) can be given intramuscularly followed by glucose per mouth. If the patient is not conscious enough to swallow glucose, subcutaneous and intravenous or per rectal administration can be used.

Conclusions. 1. The most important feature in the management of diabetics is the dietetic treatment.

2. The optimal diabetic diet should contain a minimum of carbohydrate, just sufficient protein to maintain nitrogen equilibrium, the greatest amount of fat possible within the limit of ketosis and sufficient total calories to satisfy the basal requirement.

3. The efficacy of such a diet is borne out by the clinical results obtained.

4. Such a diet is economical for two reasons: First, the diabetic with the glucose tolerance of 50 or more grams can be maintained on a diet sufficient in total number of calories to be compatible with earning a livelihood in which the amount of activity required is not excessive; secondly, the diabetic with an insufficient glucose tolerance can be maintained on an adequate diet with fewer number of insulin units and thereby less financial drain.

5. Insulin is a wonderful adjunct in the treatment of severe cases of diabetes.

6. Insulin is a specific in the treatment of uncomplicated cases of diabetic coma.

7. A treatment for cases in diabetic coma is presented.

8. Hypoglycemic reactions should be avoided but can be easily remedied when they occur.

NOTE.—The author wishes to express his most sincere thanks to Dr. Roger S. Morris for the privilege of working with insulin and for his interest in directing the investigation during its course. The insulin used was supplied gratis to the Medical Clinic by the Eli Lilly Company from November 1, 1922 to January 16, 1923. Thereafter it was bought from the Lilly Company by the hospital, which now has accumulated a special fund for the purpose, due to generous Cincinnatians and Cincinnati Organizations.

The cases studied were those which entered the Medical Service. One case from the Pediatric Service is presented by the courtesy of Dr. Kenneth Blackfan. After November 1, 1922, the cases entered the service of Dr. Mark A. Brown, to whom the author is grateful for numerous suggestions.

BIBLIOGRAPHY.

1. Banting, F. G. and Best, C. H.: The Internal Secretion of the Pancreas, Jour. Lab. and Clin. Med., 1922, 7, 251.
2. Banting, F. G. and Best, C. H.: Pancreatic Extracts, Jour. Lab. and Clin. Med., 1922, 8, 464.
3. Collip, J. B.: Preparation of Pancreatic Extracts Containing Insulin, Tr. Royal Soc. of Canada, 1922, 16.
4. Banting, F. G., Campbell, W. R. and Fletcher, A. A.: Further Clinical Experience with Insulin, Brit. Med. Jour., January 6, 1923, p. 8.
5. Woodyatt, R. T.: Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med., 1921, 28, 125.
6. Wilder, R. M., Boothby, W. M. and Beeler, Carol: Studies of the Metabolism of Diabetes, Jour. Biol. Chem., 1922, 51, 311.
7. Wilder, R. M.: Optimal Food Mixtures for Diabetic Patients, Jour. Am. Med. Assn., 1922, 78, 1878.
8. Marsh, P. L., Newburgh, L. H. and Holly, L. E.: The Nitrogen Requirement for Maintenance in Diabetes Mellitus, Arch. Int. Med., 1922, 29, 97.
9. Newburgh, L. H. and Marsh, P. L.: The Use of a High-fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med., 1920, 26, 647.
10. Shaffer, P. A.: Antiketogenesis I and II, Jour. Biol. Chem., 1921, 47, 433.
11. Shaffer, P. A.: The Ketogenic-Antiketogenic Balance in Man and Its Significance in Diabetes, Jour. Biol. Chem., 1922, 54, 399.
12. Newburgh, L. H. and Marsh, Phil.: Further Observations on the Use of a High-fat Diet in the Treatment of Diabetes Mellitus, Arch. Int. Med., 1923, 31, 455.
13. Wilder, R. M. and Winter, M. D.: The Threshold of Ketogenesis, Jour. Biol. Chem., 1922, 52, 393.
14. Hubbard, R. S. and Wright, F. R.: Studies on the Acetonuria Produced by Diets Containing Large Amounts of Fat, Jour. Biol. Chem., 1922, 1, 361.
15. Benedict, F. G.: Influence of Inanition, Carnegie Inst., Washington, D. C., 1907, Pub. 77, p. 476.
16. Lusk, G.: Science of Nutrition, Philadelphia, 1920.

POSTOPERATIVE MASSIVE PULMONARY COLLAPSE AND DROWNED LUNG.*

BY SIMON S. LEOPOLD, M.D.,

PHILADELPHIA, PA.

THE importance of postoperative pulmonary complications is appreciated, when it is realized that irrespective of the operation, or the anesthetic, one person in every fifty operated upon will develop some postoperative pulmonary complication.¹

It is my purpose to consider only one of these: the condition commonly called Massive Collapse of the Lung.

Thirty-three years ago, William Pasteur² recognized and described massive pulmonary collapse found postmortem in fatal cases of diphtheria. He believed that this condition resulted from diaphragmatic paralysis. Five years later, he described its symptoms and physical findings in patients who had postdiphtheritic multiple paralysis.³ In 1908, Pasteur, in the Bradshaw lecture,⁴ first described massive pulmonary collapse occurring as a postoperative complication. This, and three subsequent publications, in 1910,⁵ 1911⁶ and 1914,⁷ carefully and fully described this postoperative complication, and established it, as a not uncommon clinical entity. His contributions furnished the impetus for many others to record similar cases, which since that time, have appeared in increasing numbers in the literature and in the diagnoses of hospital records.

Many authors have differed greatly from Pasteur, as to the mechanism whereby postoperative pulmonary collapse is produced, but none have been able either to modify or amplify the clinical picture. His work is all the more noteworthy in that his early observations were, by necessity, unaided by the roentgen-ray or fluoroscope.

The four patients with so-called postoperative massive collapse of the lung whom I have been privileged to study, were observed at the Base Hospital at Camp Dix, New Jersey, during the time when it was my duty to see, in consultation with the Surgical Service, the cases of postoperative pulmonary complications.

It is remarkable, I think, that all of them were encountered within a period of sixteen days. Either this is a coincidence or a confession that many were overlooked, the latter probably being the correct interpretation. Perhaps this will serve as a plea for others to remember that this is not a rare condition and to keep it in mind when called upon to see cases of postoperative pneumonia, some of which surely will be found to belong to this group. It is interesting in this connection to note that Pasteur,⁷ writing in the *British Journal of Surgery* in 1914, states: "The surgical records

* Read before the John Morgan Society, April, 6, 1923.

of the Middlesex Hospital furnished no examples of massive collapse, before 1908, when I first drew attention to it. Since then, there has been a gradual increase in the number of cases, and a corresponding decrease in those of postoperative pneumonia."

Cutler and Hunt⁸ studied the postoperative pulmonary complications at the Peter Bent Brigham Hospital in 1919, and again in 1920,⁹ in which year 63 pulmonary complications in 1604 surgical cases were found. The authors stated that no cases of massive collapse were noted in either survey.

Whipple,¹⁰ who states that his interest in postoperative pulmonary complications was first aroused by unusual findings in thoracic roentgen-ray studies of patients having unexplained rises of temperature on the first or second postoperative days, studied the pulmonary complications which occurred at the Presbyterian Hospital in New York, under the title of "Postoperative Pneumonitis." He reported 97 postoperative pulmonary complications. Despite thorough roentgen-ray study, no cases of massive collapse were noted and there was no reference to the subject. He commented upon the fact that only a few cases were typical pneumonias, and referred to a type which showed resolving shadows within twenty-four to forty-eight hours with transient physical signs. He considered this to be due to congestion and exudation within the alveoli without fibrin and without hepatization, a type which the French named "Maladie de Woilley," but which Whipple calls a type of pneumonitis. It seems possible that some of these cases are in reality massive pulmonary collapse.

F. A. C. Scrimger,¹¹ of Montreal, in October, 1920, reported 7 cases of postoperative pulmonary collapse before the Clinical Congress of the American College of Surgeons. In his publication, he described fully the clinical findings in these cases, illustrating his text with numerous radiographs.

My group of cases exhibit symptoms, physical signs and roentgen-ray findings, very similar to his.

CASE I.—W. C., aged twenty-nine years. Operation, February 20, 1919, for ventral hernia, subsequent to a gunshot wound of the right hypochondrium. Ether anesthesia, 10 ounces. Duration of operation, one hour and twenty-five minutes.

CASE II.—W. T., aged twenty-two years. Operation, March 7, 1919, left inguinal hernia. Ether anesthesia, 6 ounces. Duration of anesthetic, thirty minutes.

This case is of particular interest in that, although the operation was a left inguinal herniorrhaphy, the pulmonary collapse was right sided.

CASE III.—W. M., aged twenty-five years. Operation, March 7, 1919, right inguinal hernia. Ether anesthesia, 8 ounces. Duration of anesthetic, one hour and twelve minutes.



FIG. 1.—Case I, February 21. Day following operation. Diffuse dense shadow of entire right lung. No cardiac displacement.

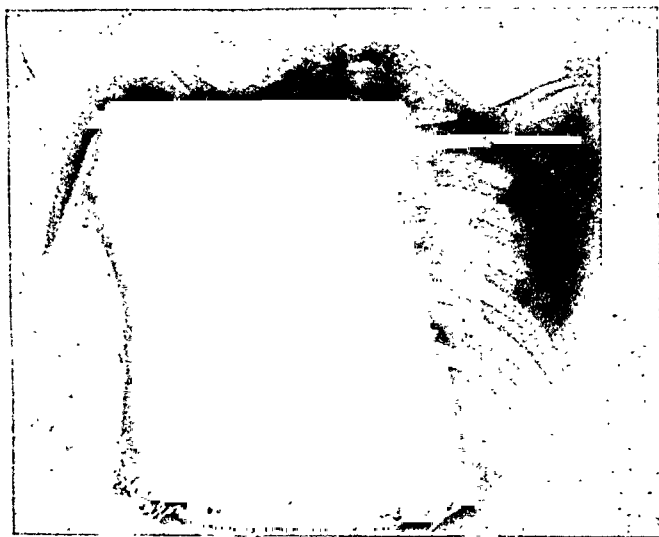


FIG. 2.—Case I, February 23. Diffuse dense shadow of entire right lung with marked cardiac displacement to the right, toward the affected side.

This case is of particular interest in that it is the only one described, to the best of my knowledge, which shows collapse, and recovery, alternately for six days, as corroborated by the symptoms, physical signs, and the radiographic findings.

CASE IV.—J. D., aged twenty-four years. Operation, February 25, 1919, left inguinal hernia. Ether anesthesia, 8 ounces. Duration of anesthesia, one hour.

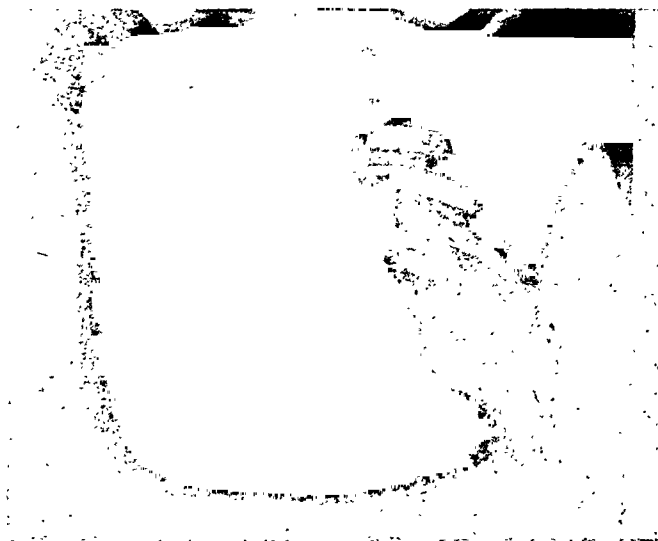


FIG. 3.—Case I, February 24. Same density of right lung, with heart shadow farther toward the left, tending to resume its normal position.



FIG. 4.—Case I, February 25. Clearing of right basal shadow with heart shadow in almost normal position. Note marked elevation of right diaphragm.

The 4 cases, which I have described, belong to the type of massive pulmonary collapse characterized by sudden onset of such severity as to suggest embolism, or acute pneumothorax. No cases of the latent type were encountered. The diagnosis of acute pneumothorax of the left side had been made in 1 of these patients (Case

I) because of the hyperresonance of the unaffected side, and the cardiac displacement toward the right.

The symptoms in these cases were of sudden onset, with marked dyspnea and cyanosis, with sharp elevation of temperature, and a disproportionately high pulse and respiratory rate.



FIG. 5.—Case I, February 26. Very marked clearing of right lung, in striking contrast to roentgen-ray of previous day. Heart in normal position. There is still some elevation of right diaphragm.



FIG. 7.—Case II, March 10. Dense shadow of entire right chest. Heart slightly displaced to the right, toward the affected side.

The physical signs were those of limitation of expansion of the affected side, with markedly diminished or absent breath sounds at the base, sometimes very distant tubular breathing toward the

apex. The heart was always displaced *toward* the affected side. All writers on the subject insist that this is *the* physical sign which must be present to establish the diagnosis. It absolutely differ-

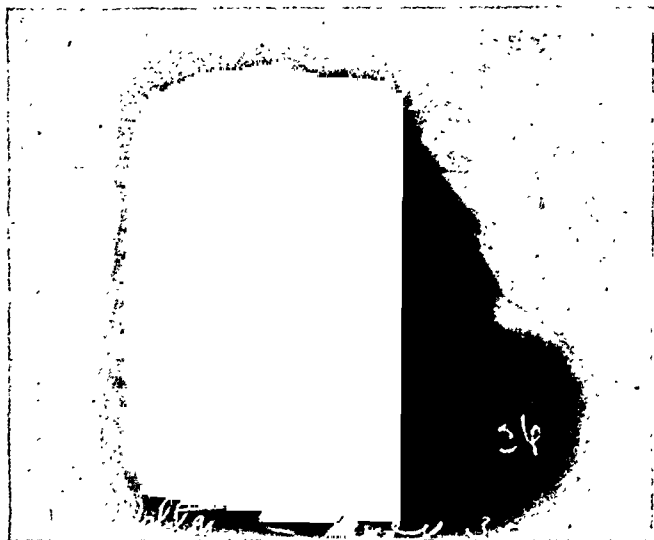


FIG. 8.—Case II, March 12. Shadow not quite so dense. Some clearing in the right lateral area. Heart shadow not so much displaced.

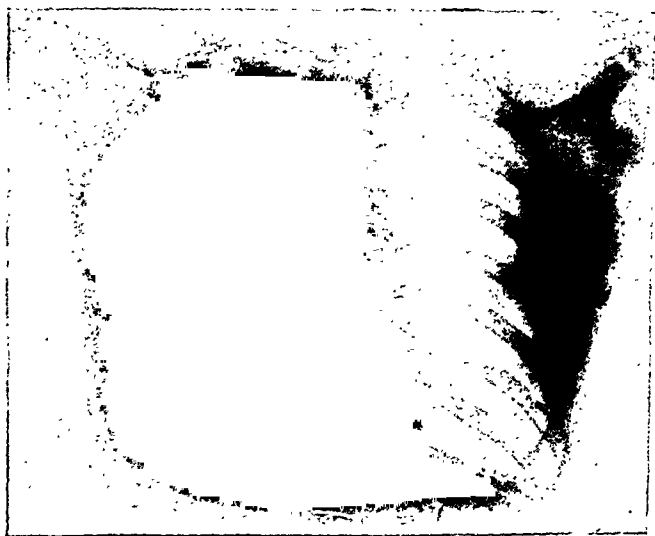


FIG. 9.—Case II, March 13. Shadow less dense, with evidence of clearing in region of the right upper lobe and laterally. Heart still displaced somewhat to the right.

entiates this condition from massive pneumonia, massive pleural effusion, and acute pneumothorax. Neither massive pneumonia nor massive effusion could possibly exhibit such remarkably sudden changes from day to day, as seen particularly in Case III, where

the pulmonary shadow appeared, and largely disappeared alternately for six days.

It is difficult to explain the sudden rise in temperature coincident with the collapse attack and the clinical chart as a whole, without

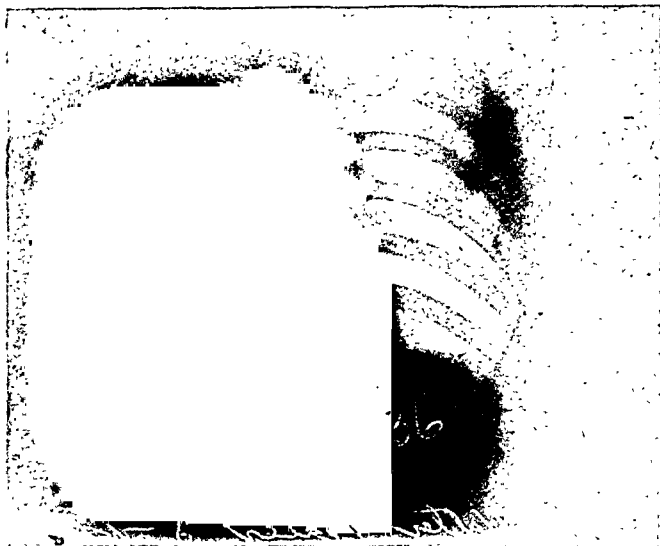


FIG. 10.—Case II, March 14. Shadow much more dense. Heart displaced a little more to the right than on previous day. A comparison with the roentgen-ray of previous day indicates a secondary collapse.



FIG. 12.—Case III, March 9. Very dense shadows of entire right chest with marked cardiac displacement *toward the affected side*.

accepting the belief that there is infection in the collapsed lung. The disproportionate rise in pulse, rate and respiration is easily accounted for on the basis of the sudden onset of the collapse with marked cardiac displacement, and severe circulatory embarrass-

ment. Case I exhibited a leukocytosis of 34,800 on the day following the collapse attack.

The first glance at the radiographs of these cases, impresses one with the absolute density of the involved lung. Not even a large

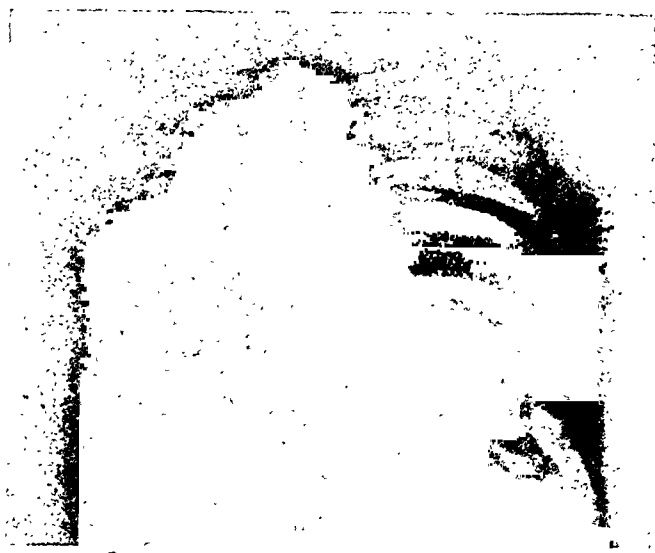


FIG. 13.—Case III, March 10. Marked evidence of clearing in area of upper lobe and laterally contrasted with roentgen-ray of previous day, with return of heart shadow to the left, almost to its normal position.

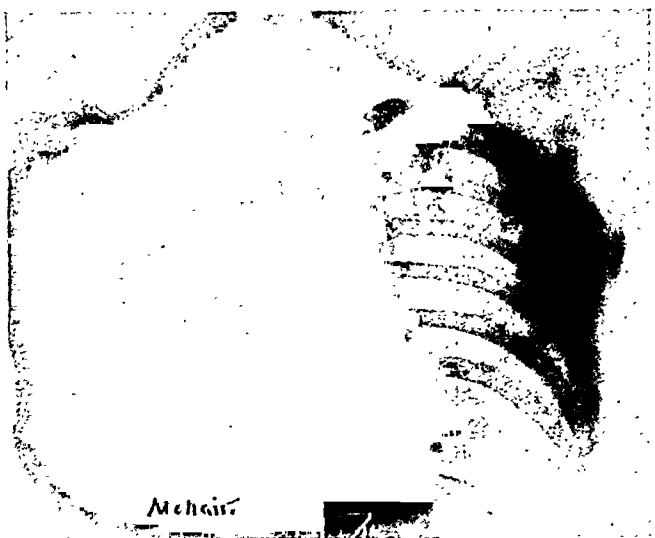


FIG. 14.—Case III, March 11. Recurrence of dense shadow of right chest, with heart greatly displaced toward the right. Very similar to Fig. 12.

empyema obscures the rib shadows so completely. It seems that there must be more than pulmonary collapse present to explain these unusual radiographs. Massive pleural effusion is eliminated as a possibility, because the cardiac displacement is toward the

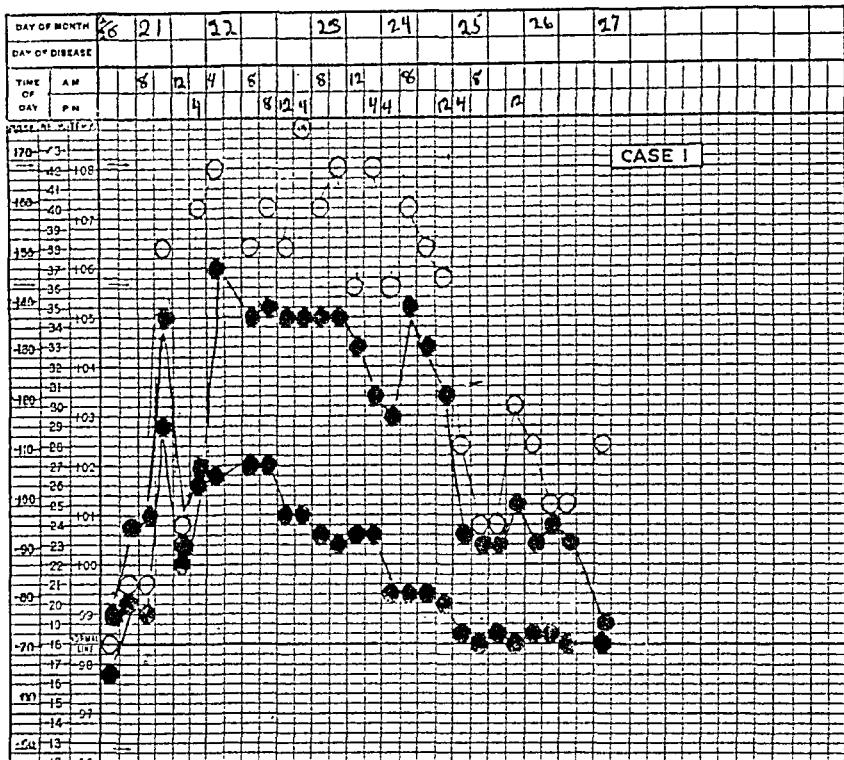


FIG. 6.—Case I, clinical chart. There was a sharp rise of temperature to 103° F., pulse 136, respiration 38, on day following operation. This was coincident with the "collapse attack." Note return of temperature to normal with sharp drop of pulse-rate and respiratory-rate on February 24, when roentgen-ray still showed marked density of entire right lung.

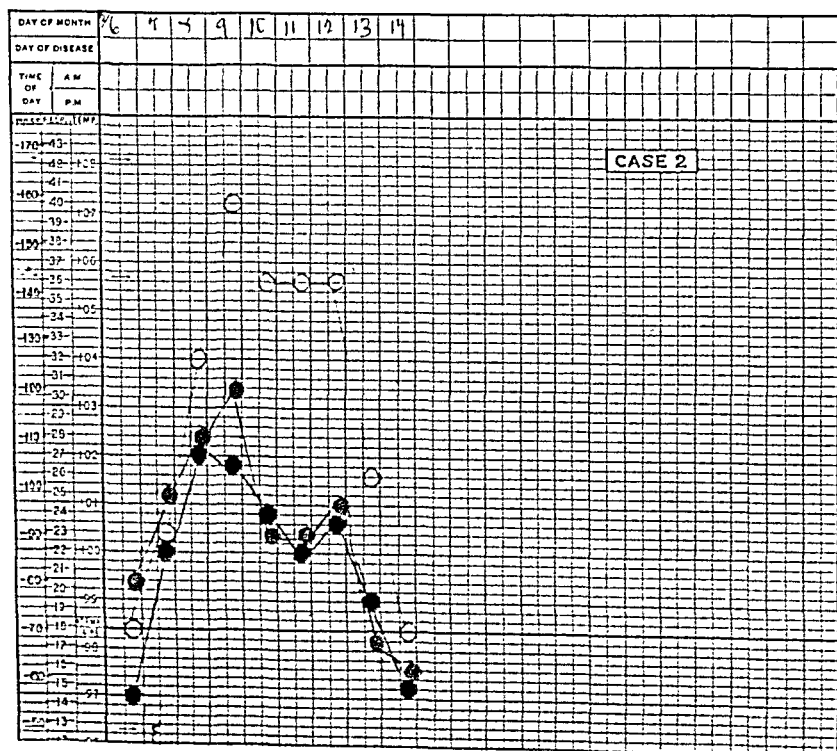


FIG. 11.—Case II, clinical chart. "Collapse attack," probably occurred March 8, the day following operation, at which time the temperature rose to 102° F., pulse 110, respiration 32. On March 14 the temperature, pulse and respiration were normal, despite the extensive lesions seen in the roentgen-ray, which shows greater density of the right lung than that of the previous day.

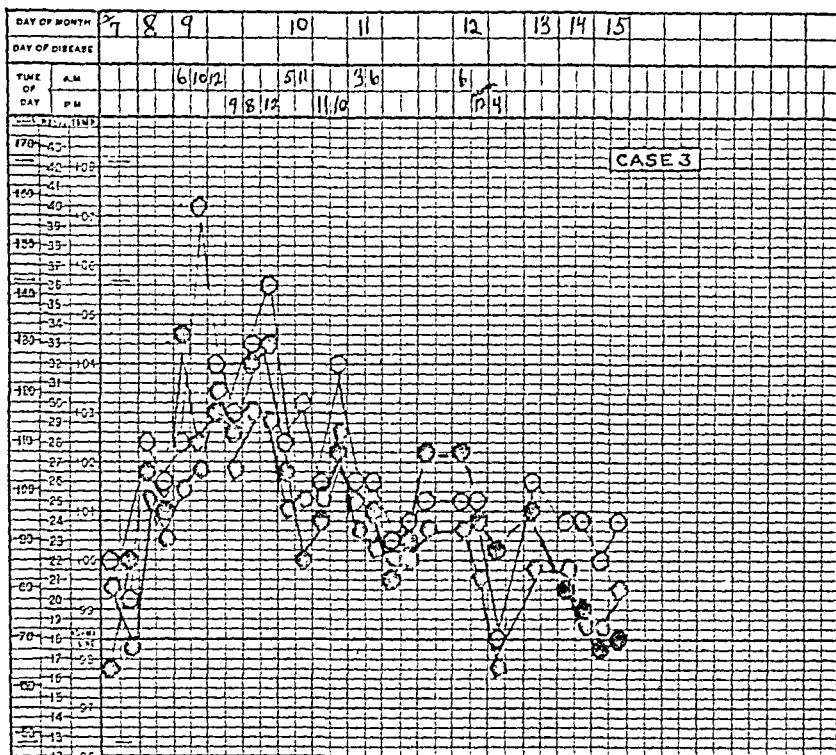


FIG. 18.—Case III, clinical chart. "Collapse attack," occurred March 8, the day following operation. It is interesting to note that the rises of temperature, pulse and respiration occurred coincidentally with the times that the radiographs showed dense shadowing and that the remissions correspond to the times when the radiographs showed marked clearing of the shadow and the return of the heart toward its normal position.

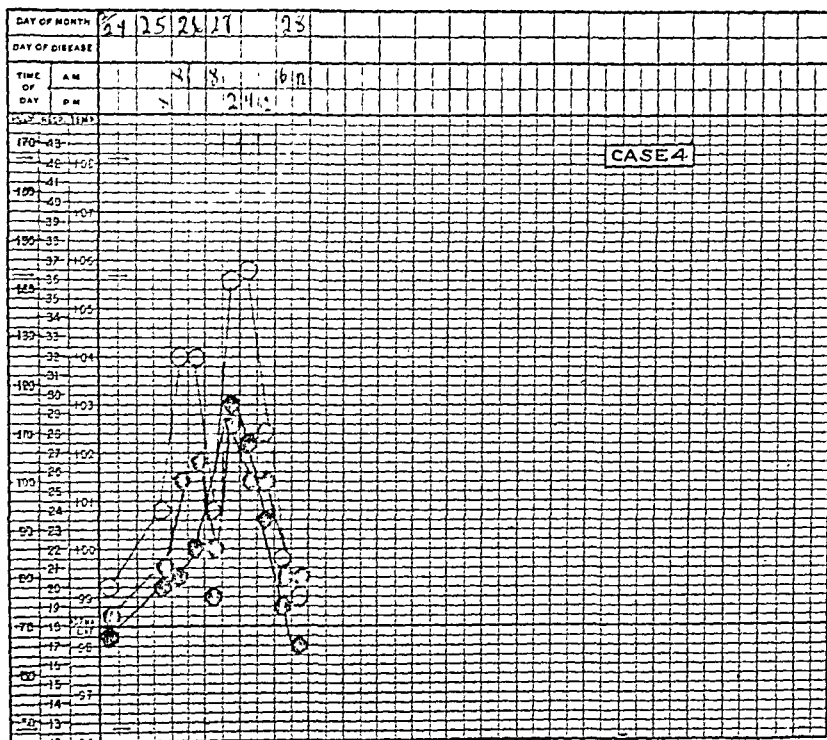


FIG. 21.—Case IV, clinical chart. Typical chart with elevation of temperature, pulse and respiration. Note that the entire duration of the postoperative complications was two days.

affected side, and is impossible, when we take into consideration comparative daily roentgen-rays. A small amount of fluid, which has no great bearing on the condition may possibly have been present. Because of the position of the heart, exploratory pleural puncture was not done.



FIG. 15.—Case III, March 12. Remarkable clearing of shadow contrasted with previous day. Heart less displaced than in Fig. 14.

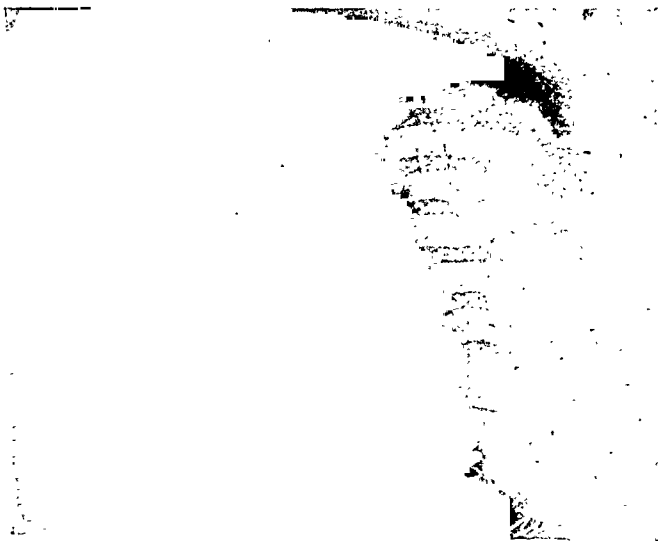


FIG. 16.—Case III, March 13. Extremely dense shadow as in Figs. 12 and 14, with similar cardiac displacement,

The most likely assumption, on which to explain the extraordinary roentgen-ray density, all things being considered, is that there is retention of secretions (fluid) within the collapsed lung.

Chevalier Jackson,¹² in the most recent edition of his book, on Bronchoscopy and Esophagoscopy, reproduces a radiograph showing the lodgment of a foreign body, the foot of an alarm clock, in the left main bronchus. The left lung is diffusely opaque and the



FIG. 17.—Case III, March 14. Marked clearly in area over upper lobe and laterally very similar to Figs. 13 and 15, with heart shadow nearly in its normal position.

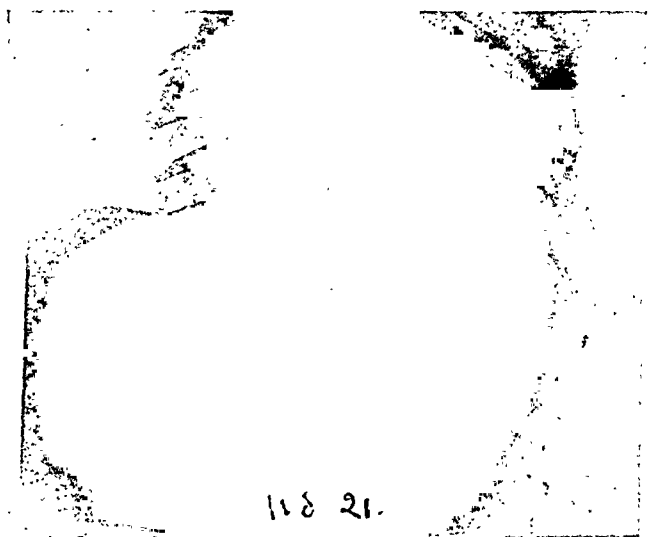


FIG. 19.—Case IV, February 26. Dense shadow, lower left chest. Heart displaced toward affected side.

cardiac shadow is definitely displaced toward the left (the affected side). He describes this as "atelectasis and drowned lung," a diagnosis based on direct bronchoscopic observation.

Unfortunately, there were no facilities to do direct bronchoscopy on any of these cases, nor have I been able to find a record of it

having been done in any of the cases of postoperative collapse, but pending the appearance of the next case, which Dr. Jackson is very eager to bronchoscope, I should like to adopt Dr. Jackson's words, "drowned lung," and apply them to this condition, and consider that these cases are best described as "*postoperative massive pulmonary collapse and drowned lung.*"

Postoperative massive collapse of the lung, that which I am pleased to term massive collapse and drowned lung, has been accepted as a definite clinical entity since Pasteur's brilliant contributions, but the mechanism whereby this condition is produced has always been a subject of controversy, and so remains.

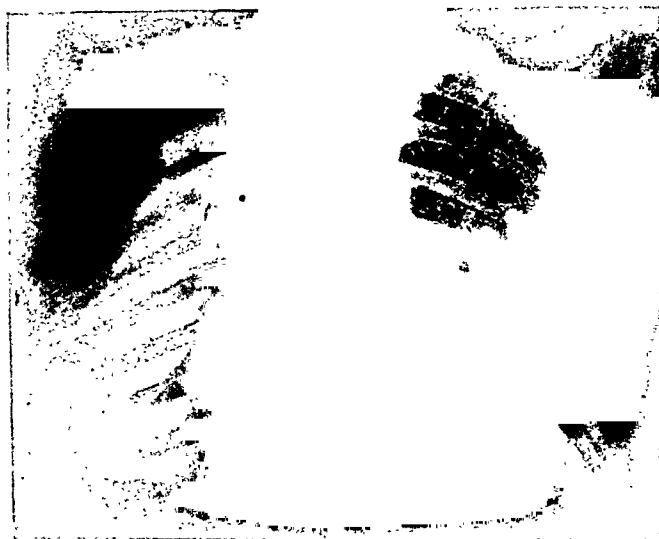


FIG. 20.—Case IV, February 27. Involved area much clearer. Heart in normal position.

Pasteur⁵ believes that it is due to an active collapse, the result of some deflating force which compresses and empties the lung in the absence of any obstruction of the airway, and attributes it to paralysis of the diaphragm and intercostals. That this explanation is not tenable for all cases is certain, for many reasons. According to Briscoe¹³ and others, diaphragmatic paralysis, due to phrenic nerve injury, does not reproduce this picture. Secondly, it was pointed out by Elliott and Dingley,¹⁴ that if the condition was due to active pulmonary collapse, it would have to be assumed that the alveolar walls have active contractile power, which assumption has no support in present physiology.

If this were true, however, Elliott and Dingley maintain that the pressure on the affected side would be higher and the heart would be displaced away from the affected side. We know that this does not occur.

Lichtheim,¹⁵ in 1878, studied the subject of pulmonary collapse by introducing into the bronchi of rabbits laminaria plugs, without

opening the thorax. As the plug swelled, the lung behind it collapsed. He found that collapse did not occur when the pulmonary vessels were tied. He, therefore, concluded that collapse occurred by the absorption of the alveolar air into the blood. From this Elliott and Dingley conclude that the bronchus becomes blocked with secretion, then the air contained in the lung is absorbed into the blood, creating, to phrase it roughly, a vacuum, which causes the diaphragm to rise and the heart to be displaced toward it. The early occurrence of viscid expectoration, as a usual symptom in these cases, suggests that the bronchus has been plugged with this secretion.

If bronchoscopical examination during a collapse attack will demonstrate complete bronchial obstruction in the bronchus supplying the collapsed and "drowned lung," then this explanation would seem correct, for those cases which occur postoperatively. It does not, however, explain all cases of massive collapse.

Sir John Rose Bradford¹⁶ calls attention to the fact that massive collapse of the lung may occur in a variety of ways other than postoperatively. It may occur as the result of a gunshot wound of the chest wall, where no anesthetic has been given, where no penetration has occurred, and where the wound is so slight that patients are not confined to bed prior to the collapse attack. He states that massive collapse occurs in 5 to 10 per cent of all cases of gunshot wounds of the chest. It may be homolateral or contralateral, and often follows trivial injury without penetration of the pleura. It may also follow severe injuries, such as fracture of the pelvis and femur where there has been no chest injury.

If postoperative massive collapse and drowned lung has a pathology distinct and separate from that of massive pulmonary collapse occurring from other causes, then the opinion of Elliott and Dingley, that the postoperative type is due to bronchial obstruction, is probably correct. Direct bronchoscopy during a collapse attack should decide the question. No explanation has been offered to explain massive collapse occurring under the conditions which Sir John Rose Bradford describes.

It is my belief that the two conditions are dissimilar, each having a different cause. The former is probably due to bronchial obstruction with resulting atelectasis and drowned lung, the latter a simple atelectasis, without bronchial obstruction and without drowned lung. Perhaps it will be found that the latter results from some sudden vasomotor disturbance.

Summary. Four cases of postoperative massive pulmonary collapse are presented, each with comparative roentgen-rays and clinical charts.

The extreme radiographic density of the pulmonary tissue makes it necessary to consider this condition to be more than simple massive atelectasis.

The opinion is advanced that "massive collapse and drowned

lung" exist and that the radiographic findings are thus better explained.

Complete bronchial obstruction offers the best explanation for the cause of this condition, despite the fact that direct bronchoscopy during a collapse attack has not been done in any of these cases.

Pulmonary collapse occurring under conditions other than those seen postoperatively, is probably pure atelectasis, without drowned lung, and has a different cause, which may be a sudden vasomotor disturbance.

It would appear that massive collapse and drowned lung are more common than the surveys of postoperative pulmonary complications would indicate, and that the possibility of its occurrence should always be kept in mind, especially when called upon to see "postoperative pneumonia."

The recognition of these cases is of great importance, as their prognosis is vastly better than that of postoperative pneumonia, embolism, and acute pneumothorax—the conditions with which massive collapse and drowned lung are most frequently confused.

I desire to express my great indebtedness to Captain Robert Shoemaker, M.C., U. S. A., for taking the radiographs which are here reproduced; to Dr. Henry Pancoast, who, in the absence of Captain Shoemaker, interpreted them for me, and to Dr. Chevalier Jackson for his kindly criticism and advice.

REFERENCES.

1. Pepper, O. H. P.: Postoperative Pulmonary Complications with Three Illustrative Cases, *Med. Clin. North America*, 1921, 5, 737.
2. Pasteur, William: Respiratory Paralysis after Diphtheria as a Cause of Pulmonary Complications, *AM. JOUR. MED. SCI.*, 1890, 100, 242.
3. Pasteur, William: Cases Illustrating the Association of Respiratory Paralysis with Cardio-pulmonary Symptoms in Diphtheritic Multiple Paralysis, *Trans. Clin. Soc., London*, 1895, 28, 111.
4. Pasteur, William: Massive Collapse of the Lung, *Lancet*, 1908, 2, 1351.
5. Pasteur, William: Active Lobar Collapse of the Lung after Abdominal Operations, *Lancet*, 1910, 2, 1080.
6. Pasteur, William: Postoperative Lung Complications, *Lancet*, 1911, 1, 1329.
7. Pasteur, William: Massive Collapse of the Lung, *British Jour. Surg.*, 1914, 1, 587.
8. Cutler, E. C., and Hunt, A. M.: Postoperative Pulmonary Complications, *Arch. Surg.*, 1920, 1, 114.
9. Cutler, E. C., and Hunt, A. M.: Postoperative Pulmonary Complications, *Arch. Int. Med.*, 1922, 29, 449.
10. Whipple, A. O.: A Study of Postoperative Pneumonitis, *Surg., Gynec. and Obst.*, 1918, 26, 29.
11. Scrimger, F. A. C.: Postoperative Massive Collapse of the Lung, *Surg., Gynec. and Obst.*, 1921, 32, 486.
12. Jackson, Chevalier: Bronchoscopy and Esophagoscopy; a Manual of Peroral Endoscopy and Laryngeal Surgery, W. B. Saunders Company, 1922, p. 140.
13. Briscoe, J. C.: The Mechanism of Postoperative Massive Collapse of the Lungs, *Quart. Jour. Med.*, 1920, 13, 293.
14. Elliott, T. R., and Dingley, L. A.: Massive Collapse of the Lungs Following Abdominal Operations, *Lancet*, 1914, 1, 1305.
15. Lichtheim: Versuche über Lungenat elektase, *Arch. f. exper. Path. u. Pharmacol.*, 1879, 10, 54.
16. Bradford, Sir John Rose: *Oxford Med.*, 1920, 2, 127.

A CASE OF PRIMARY CARCINOMA OF THE BLADDER WITH METASTASIS TO THE BRAIN.

BY WILLIAM E. LOWER, M.D.,

AND

RALPH M. WATKINS, M.D.,

CLEVELAND CLINIC, CLEVELAND, OHIO.

IN a careful search of the literature we have not been able to find that any case in which a metastasis in the brain has developed from a primary carcinoma in the bladder has ever been reported. Therefore an encounter with a case in which the tissue from a growth in the brain was of the same nature as that of an original growth in the bladder makes it seem worth while to publish this report.

Case Report. The patient, a male, white, aged forty-eight years, entered the Cleveland Clinic on April 19, 1922. Except for the death of an older sister from tuberculosis his family history was negative. He had been married eight years and had one child. His past health had been fairly good. He had had pneumonia at the age of six years, scarlatina at ten, a small hernia and varicocele (never operated upon) while in college; and during the immediately preceding years, several attacks of tonsillitis. His habits were fairly good: a moderate use of alcohol, but no tobacco and no coffee.

The patient reported at the Clinic because of difficulty in urinating. Ten months before this, life insurance had been granted him in spite of the presence at the time of some bladder irritation; but three months after that examination he had failed to pass another examination for insurance because of the presence of blood and albumin in the urine. A physician prescribed a special diet and asked him to report again in a month. He had not improved, and his tonsils and a nasal growth were held to account for his condition. About April 1, he had a sharp attack of hematuria following horse-back riding. A cystoscopical examination by Dr. Louis E. Schmidt of Chicago, disclosed a bladder tumor, probably malignant. When he came to the Clinic he was having some difficulty in emptying the bladder, and showed also a little loss of control of his left foot and a slight speech defect.

Physical Examination. The patient was a well-nourished man, weight 185 pounds, height 5 feet 10 inches. The skin was a trifle pale, but showed no rashes; pupils equal, regular, reacted well to light, no ocular palsy; glasses worn for myopia; teeth showed a great deal of dental work but were in good condition; pharynx red; tonsils chronically inflamed; tongue slightly coated; nasal septum was markedly deflected by old trauma; no thyroid nor glandular enlargement; lungs normal; heart, aorta, and palpable arteries normal; pulse rate 70; blood-pressure 140-95; no tenderness nor

masses in abdomen, and no palpable enlargement of organs; small left inguinal hernia; extremities negative; reflexes equal and active. Roentgen-ray examinations of the skull and pelvis were negative.

A cystoscopical examination revealed a round fungating tumor just inside the internal sphincter slightly to the right of the median

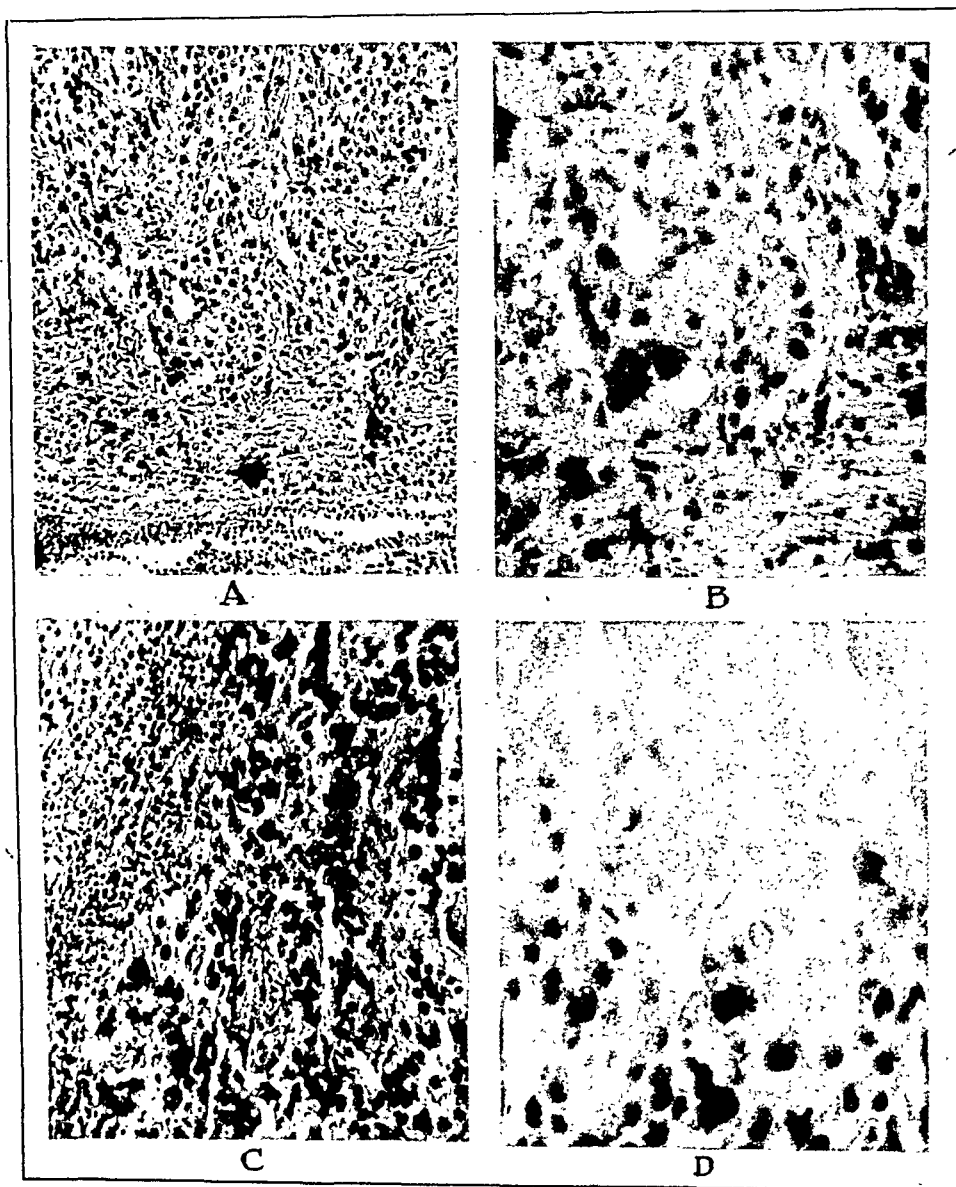


FIG. 1.—A, carcinoma of the bladder (low \times); B, carcinoma of the bladder (high \times); C, metastasis to the brain (low \times); D, metastasis to the brain (high \times).

line; the whole tumor could not be seen in one field of the instrument. The urine showed 30 to 50 erythrocytes per field, and a great many pus cells; the blood count showed 5,020,000 red cells, 7200 white cells, and 75 per cent hemoglobin. The phenolsulphonephthalein test showed a total elimination of 45 per cent—

25 per cent the first hour and 20 per cent the second hour. The blood Wassermann test was negative.

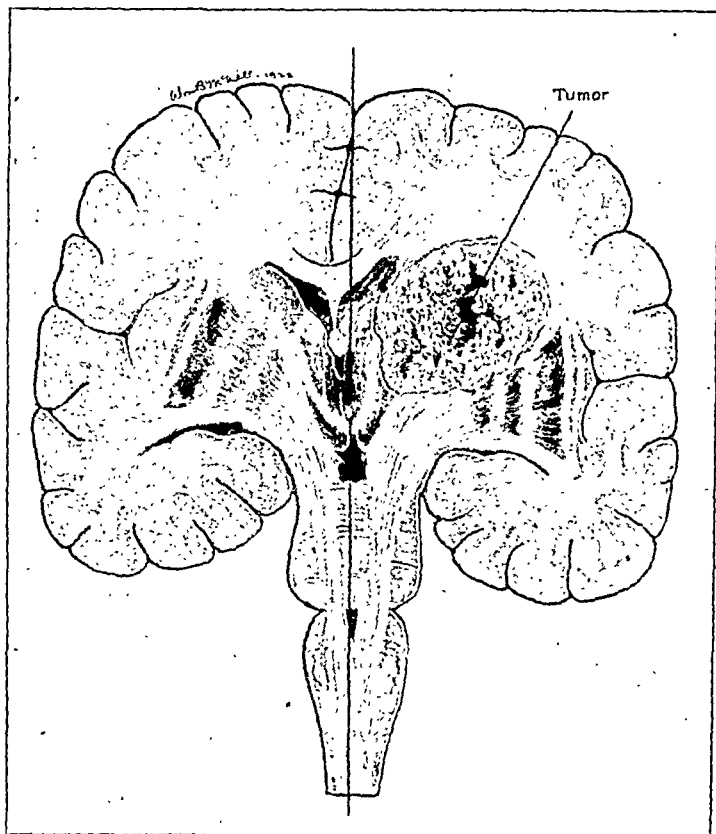


FIG. 2.—Schema, showing position of brain metastasis.



FIG. 3.—Brain metastasis.

The possibility that there might be also a tumor of the brain was considered at this time, but since the eye-ground examination and the roentgen-ray examination of the skull were negative, this opinion was not supported.

On April 24, the growth in the bladder was removed by a suprapubic incision. Because of the apparent malignancy, 65 mg. of radium were applied for six hours at the seat of the tumor. Healing was uninterrupted.

Gross Pathology of Bladder Tumor. The tumor was $1\frac{1}{2}$ cm. in diameter, rounded, firm, with a fairly small pedunculated base surrounded by a section of the bladder wall.

Histo-pathology of Bladder Tumor. The sections show a rather loose connective-tissue stroma largely invaded by malignant transitional epithelial cells. There is a tendency for the masses of tumor cells to form alveoli. These tumor cells are arranged around a connective-tissue base as if pedunculated and in this connective tissue are epithelial lined spaces which are either dilated ducts or acini which are benign (Fig. 1, A and B).

Pathological Diagnosis: Transitional-cell carcinoma of the urinary bladder.

A short time after the removal of the bladder tumor the difficulty in walking and the speech defect became more pronounced and a clinical diagnosis of brain tumor was made.

On June 6, 1922, six weeks after the bladder operation, Dr. Walter E. Dandy, of Baltimore, removed from the right internal capsule, a circumscribed tumor which he believed to be a metastatic carcinoma (Fig. 2). The patient made an excellent recovery from the operation.

Gross Pathology of the Metastatic Tumor. The tumor was rather firm in consistency and about 2 cm. in diameter. It was generally spherical in shape, with a rather irregular surface. The color was light gray; there was little gross increased vascularity. It cut like a very cellular tumor and on section, seemed to be entirely encapsulated. The central tissue was soft, friable, and apparently somewhat degenerated. It had many small papillary projections (Fig. 3).

Histo-pathology of Metastatic Tumor. The sections show essentially the same picture as those presented by the bladder tumor. The epithelial cells are malignant, are of the transitional type, and like those of the primary tumor have a tendency to group themselves in alveoli. The stroma consists of neuroglia tissue.

Pathological Diagnosis of Metastatic Tumor: Transitional-celled carcinoma of the brain, metastatic from carcinoma of the bladder.

On November 8, 1922, seven months after the removal of the bladder tumor a cystoscopical examination disclosed a suspicious area in the region of previous growth. Another examination on February 12, 1923, ten months after the operation, showed that the bladder was free from any signs of recurrence. At this time there was still some paralysis of the left arm and leg and the difficulty in speech had increased. The patient died early in April, 1923, ten months after the removal of the brain tumor, the cause of death being a recurrence of the brain metastasis.

REVIEWS.

A MANUAL OF THE PRACTICE OF MEDICINE. By A. A. STEVENS, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania; Visiting Physician to the Philadelphia General Hospital. Prepared especially for students. Eleventh edition, entirely reset. Pp. 645; 16 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

ALTHOUGH too brief and sketchy in character for the routine use of the modern fourth year medical student it would seem that this manual, which is certainly the standard one in English, is ideally suited for the first and second years, especially since an effort is now being made to introduce the clinical subjects in outline at that time. It also has a value in that it affords older students and physicians a means of rapidly reviewing the entire subject of medicine. The reviewer has found it of signal help also in the instruction of nurses. Its accuracy is guaranteed by Dr. Stevens' experience as a teacher and practitioner and by the eleven editions within thirty-one years.

M.

HELIO THERAPY. By A. ROLLIER, M.D., Medical Director of the Institutions for Heliotherapy, Leysin; Laureate of the Academy of Medicine, Paris; Correspondent Member of Societies of Medicine and Pediatrics, Paris. With the Collaboration of A. ROSSELET, D.Sc., Lecturer on Physiotherapy, Geneva University; formerly Assistant at Rollier's Institutions, Leysin. H. J. SCHMID, M.D., Radiologist at Rollier's Institutions, Leysin; and E. AMSTAD, M.D., Surgeon at Rollier's Institution, Leysin. With Forwards by SIR JOHN HENRY GAUVAIN, M.A., M.D., M.R.C.S., L.R.C.P., and CALEB WILLIAM SALEEBY, M.D., F.R.C.S. Pp. 288; 52 illustrations. London; Henry Frowde, Hodder & Stoughton (Oxford Medical Publications), 1923.

HELIO THERAPY, because of its recent resurrection from great antiquity is considered a modern therapeutic agent. Dr. Rollier's enthusiasm is infectious. He clearly states the indications and contraindications to heliotherapy and considers it a curative agent in surgical tuberculosis (bone and joints), but he goes a bit beyond

his scope when he sights a case of diabetes mellitus, in which glycosuria was controlled by exposure to sunlight. One hundred and eight pages are devoted to case reports that were cured at the author's institutions, which seem much like testimonials. No mention is made of failures. The chapters on the "Scientific Basis of Heliotherapy," the "Radiological Diagnosis of Osteoarticular Tuberculosis and the Radiographic Control of the Clinical Results of Heliotherapy" and "The Adjuvants of Heliotherapy" are well written. The book has a distinct niche in medical literature as a stepping stone to a more exhaustive treatise of a subject not yet fully appreciated. L.

PRINCIPALS AND PRACTICE OF INFANT FEEDING. By JULIUS HESS. Third edition. Pp. 496; 34 illustrations. Philadelphia: F. A. Davis Company, 1923.

IN the third edition of his already well-known manual on infant feeding, Hess has enlarged upon the commonly met symptoms in infancy. He has also added chapters dealing with the diseases of metabolism.

The book is concise, complete and most handy for ready reference for teacher, student or practitioner. It is well illustrated by nicely selected clinical cases and records.

This book deserves a readily accessible space among text-books. D.

MENTAL DEFICIENCY (AMENTIA). By A. F. TREDGOLD, M.D., M.R.C.P., F.R.S., (EDIN.), Lecturer on Mental Deficiency at the London University. Fourth edition. Pp. 569; 30 illustrations. New York: William Wood & Co., 1922.

THIS is the fourth edition of this well-known work and it consists of twenty-two chapters with an appendix and index, eighteen tables and thirty illustrations.

The first three chapters are largely introductory. The next four chapters are given to a discussion of pathology, classification, neurophysiology and psychology and the physical characteristics of amentia. The remainder of the book takes up various forms of amentia, its diagnosis and prognosis and the various forms of treatment.

The illustrations are excellent but the type is rather small. From a scientific point of view Tredgold has written an excellent book in which mental deficiency is discussed from every angle. The style is easy and the book should be in the library of every up-to-date physician. W.

LOCAL ANESTHESIA METHODS AND RESULTS IN ABDOMINAL SURGERY. By PROF. DR. HANS FINSTERER, Surgeon-in-Chief, Vienna Hospital of the Brothers of Charity. Authorized English version by JOSEPH P. F. BURKE, M.D., Sc.D., LL.D., Attending Surgeon, Buffalo Hospital of the Sisters of Charity. Pp. 331; 42 illustrations. New York: Rebman Company, 1923.

THE markedly successful results with various forms of local and conductive anesthesia in the hands of the author are presented to the English reader in an excellent translation by his pupil, the translator. The first part of the book discusses the general considerations, the indications and technic of the various forms of conductive anesthesia. The second part of the book deals with the application of these methods in abdominal surgery, gynecology and urology. Many case histories are used in detailing the different modes of procedure. The book closes with a full and up-to-date bibliography, with an unusually large number of American references.

W.

MISTAKES AND ACCIDENTS OF SURGERY. By HAROLD BURROWS, C.B.E., M.B., B.S. (LOND.), F.R.C.S., Assistant Surgeon with the British Expeditionary Force in France; Late Hunterian Professor of Surgery at the Royal College of Surgeons of England. Pp. 470. New York: William Wood & Co., 1923.

THERE is a wealth of clinical wisdom in the pages of this little book. It is not a resultory account of interesting or amusing errors of omission or commission. The author systematically reviews the whole subject of regional surgery with reference to the chief pitfalls of judgment and technic. Such a book is born of long experience only. The embryo surgeon would do well to read and consider; the more mature will be diverted and fortified in many conclusions gained from his masters or learned in a harder school.

P.

FUNCTIONAL AND NERVOUS DISORDERS. Their Classification and Treatment. By DONALD E. CORE, M.D., Lecturer in Neurology, University of Manchester, England. Pp. 371; 21 illustrations. New York: William Wood & Co.

THIS book is divided into six parts; taking up in order general considerations, the regressive group of the functional nervous disorders, the progressive or sympathetic nervous disorders, some considerations regarding the functional nervous disorders in general, diagnosis and prognosis, and lastly treatment. In this work on

functional nervous disorders Core has given to the profession an excellent book on the diagnosis and treatment of the psychoneuroses. The chapters on treatment are full of excellent ideas for the handling of a very difficult group of cases. Core recognizes, as most neuro-psychiatrists do, that the sex instinct can bring about a neurosis, but that it is not responsible for the vast majority of functional nervous disorders. One might express surprise that the epoch making writings of Babinski in regard to hysteria are not more frequently mentioned. W.

INTRODUCTION TO MEDICAL BIOMETRY AND STATISTICS. By RAYMOND PEARL, Professor of Biometry and Vital Statistics in the School of Hygiene and Public Health and of Biology in the Medical School, Johns Hopkins University. Pp. 379; 71 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

THIS book will appeal primarily to the medical writer and research worker desiring to know how best to obtain and handle his statistical data. The physician who is puzzled by such terms as "skewness," "coefficient of correlation," "probable error," etc., which appear with even increasing frequency in the medical literature of the day, will likewise find this work enlightening, but difficult to understand unless he be gifted to an unusual degree with talent for mathematics. On the other hand, the expert mathematician will perhaps be disappointed in failing to find the detailed approach and the mathematical proof of many of the formulæ appearing in these pages.

A.

BLUTKRANKHEITEN UND BLUTDIAGNOSTIK. By O. NAEGELI, M.D. O. Ö. Professor der inneren Medizin an der Universität Zürich und Direktor der medizinischen Universitätsklinik. Fourth edition. Pp. 587; 62 illustrations. Berlin: Julius Springer, 1923.

THIS book is one of the standard books on the morphology of the blood cells, dealing with the pathological state of the blood and bone-marrow as well as the norm. Dr. Naegeli discusses in full and with minute detail, diseases that are associated with disturbances of the red cells, the white cells and infectious diseases. There is no mention, however, of the chemistry of the blood. This is not an oversight nor is it a fault to be criticised because the book is in no sense meant to be a complete treatise on the blood, which of course would include chemistry of the blood. It is, as the title says, merely a treatise on blood diseases and blood diagnosis, meaning the blood cells themselves. The work is the best piece of the

printer's art that we have seen from Germany since the war, the paper is of good quality, there is an absence of typographical errors and the numerous colored plates at the end of the book are beautifully executed.

M.

LABORATORY DIAGNOSIS OF SYPHILIS. By HIDEYO NOGUCHI, M.D., M.S., PH.D., D.Sc., Member of the Rockefeller Institute for Medical Research, New York, Pp. 392; 59 illustrations, of which 13 are in color. New York: Paul B. Hoeber, 1923.

THIS book aims to present the elementary principles of hemolysis and complement-fixation as applied in the serum diagnosis of syphilis, and also details methods for the identification of *Treponema pallidum*.

Emphasis is very opportunely placed upon the advantages of dark-ground illumination over staining methods for the identification of *treponema*. The principles and the technic of dark-field microscopy are very well presented. Among the staining methods, the simplified and reliable buffered-formalin method from the author's laboratory is described. Cultural methods for the *Treponema pallidum* and animal inoculations procedures for their detection are omitted.

The Wassermann reaction is presented in much the same manner as in the author's *Serum Diagnosis of Syphilis*, 3d ed., 1912, with all its inherent objectionable features passed over lightly. The practical difficulty of preparing antihuman amboceptor is mentioned, but no mention is made of the difficulties arising from the appearance of specific hemoagglutinins in such antisera. While attributing the lack of standardization of the Wassermann reaction to unknown and variable quantities of amboceptor inherent in the hetero-hemolytic systems, the author yet recommends the inaccurately gauged doses of available amboceptor used in the homo-hemolytic system in the form of serum dried on paper. In the chapter presenting the system of serum diagnosis recommended by the author no mention is made of the titration of complement.

In discussing the effects of treatment upon the Wassermann reaction, much of the material upon which the argument is based is represented by work done prior to 1912, so that statements of 1250 cases treated with salvarsan with 40 relapses; 110 cases with 3 relapses; 789 cases with 33 relapses, appear as obsolete and worthless data in the light of present-day syphilology.

The luetin reaction is presented as favorably as possible by omitting the recent more critical inquiries into its value.

An extensive bibliography is appended, but here again, so far as serology is concerned, the greater number of the references are old and chiefly of historical interest.

S.

PHYSICAL DIAGNOSIS. By W. D. ROSE, M.D., Lecturer on Physical Diagnosis and Associate Professor of Medicine in the University of Arkansas. Third edition. Pp. 755; 319 illustrations. St. Louis: C. V. Mosby Company, 1922.

DR. ROSE's book takes up first the physical examination of the thorax and respiratory organs with a very thorough consideration of percussion signs and breath sounds. The various diseases of the respiratory organs are then discussed fully. The examination of the heart is treated in a thorough manner and this section has been revised so that it includes important recent work in cardiology. The discussion of heart murmurs is exceptionally good. There is a chapter on the Diagnosis of Abnormalities of the Heart Beat, by Dr. Drew Luten. Examination of the abdomen and abdominal organs and examination of the kidneys are fully discussed and examination of the nervous system briefly treated.

This book is well written, the subject matter well divided and the illustrations numerous and well chosen. The treatment of physical signs in diseases of the lungs are especially good. This is an excellent text-book on physical diagnosis. T.

THE FORM AND FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM. AN INTRODUCTION TO THE STUDY OF NERVOUS DISEASES. By FREDERICK TILNEY, M.D., PH.D., Professor of Neurology, Columbia University, and HENRY ALSOP RILEY, A.M., M.D., Associate in Neurology, Columbia University, with a foreword by GEORGE S. HUNTINGDON, Sc.D., M.D., Professor of Anatomy, Columbia University. Second edition. Pp. 1019; 763 illustrations. New York: Paul B. Hoeber, 1923.

THE intention of the authors of this book to incorporate the anatomy and physiology of the central nervous system as essential parts of the practical knowledge necessary to the proper diagnosis and treatment of disease has been so well accomplished that this second edition has been demanded. The work has successfully brought about the result for which it was designed, namely, "To fill the gap between morphology and the practical requirements of clinical medicine; to visualize the living nervous system, to make accessible an appreciation of its vital relation to the functions; which go to make up life, as well as the defects in these relations which result in disease."

The great value of the book to every medical student, more particularly perhaps to the one who intends to take up neurology as a specialty, as noted on the appearance of the first edition, is again here stressed.

AN INTRODUCTION TO THE STUDY OF MENTAL DISORDERS. By FRANCIS M. BARNES, JR., M.A., M.D., Associate Professor of Nervous and Mental Diseases in the St. Louis University Medical School. Second edition. Pp. 295. St. Louis: C. V. Mosby Company, 1923.

THIS book is a combination of two of Dr. Barnes' former works, namely, his *Introduction to the Study of Mental Diseases* and his *Notes on Mental Diseases*, which have been revised and considerably amplified, with some entirely new chapters added, and more extended consideration given to certain types of mental disease. The new chapters have to do with the subject of mental hygiene and social psychiatry, also the mental factor in industry and vocational guidance. They are both well written, and the sound interpretation of mental hygiene very well stresses the present method of study of mental medicine, *i. e.*, the progressive mind of the psychological conception. This is well balanced by the importance paid to the non-specificity of mental disease in another chapter. The book can be heartily recommended to medical students as a brief of psychiatric fundamentals, which will be of great value to psychiatric social workers as well. G.

MINOR MALADIES. By LEONARD WILLIAMS, M.D., Physician to the French Hospital. Fifth edition. Pp. 414. New York: William Wood & Co., 1923.

THIS little book will always prove useful because the minor maladies are often the most difficult things the physician has to treat. It is full of practical suggestions and has a certain ease of presentation which is so characteristic of English medical writings. M.

THE CARE OF THE BABY. By J. P. CROZER GRIFFITH, M.D., Professor of Pediatrics in the University of Pennsylvania: Physician to the Children's Hospital and Consulting Physician to St. Christopher's Hospital for Children. Seventh edition. Pp. 478; 104 illustrations. Philadelphia: W. B. Saunders Company, 1924.

GRIFFITH's book on the care of the baby has been a standard since 1895. The fact that it has reached such an enormous circulation and is so extensively used is sufficient evidence of its value. M.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Isoagglutination in New-born Infants and Their Mothers. A Possible Relationship Between Isoagglutination and the Toxemia of Pregnancy.

—In an interesting study of the isoagglutination reaction in 180 women and their new-born infants, McQUARRIE (*Bull. Johns Hopkins Hosp.*, 1923, 34, 31) finds the blood group to be completely established at birth in 11 per cent of the infants and to be partially established in over half. The blood group of the infant might or might not be the same as that of the mother, so that McQuarrie concludes the intact placenta is impermeable to isoagglutination. Sixteen outspoken cases of eclampsia and 24 of mild or potential eclampsia were included in the study, and it is most interesting to note that over 70 per cent of these cases of toxemia occurred in the small group in which there was interagglutination between fetal and maternal blood. Toxemia occurred 165 times more frequently when the maternal and fetal bloods were demonstrated to be incompatible than when they were in the same isoagglutination group. Conclusions as to the actual importance of these findings in discovering the cause of eclampsia are withheld until further work can demonstrate some mechanism by which the fetal blood can gain access to the maternal circulation. Perhaps hardest of all to be explained will be the eclamptic seizures coming on some time after delivery. A note of warning is sounded against transfusing an infant with any blood, even its mother's, without first carefully matching for agglutination.

Studies on the Influence of Pregnancy in Syphilis. 1. The Course of Syphilitic Infection in Pregnant Women.—A clinical and laboratory study was made by MOORE (*Bull. Johns Hopkins Hosp.*, 1923, 34, 89)

of 178 pregnant women with positive blood Wassermann reactions and 22 non-pregnant mothers of syphilitic children. Pregnancy seemed to cause striking deviations from the usual course of the syphilitic infection. The early manifestations of syphilis may fail to appear if infection and impregnation appear, or if they do appear, they are much milder than is usual in non-pregnant women. This protection against the disease afforded by pregnancy often persists for many years, and in a few cases for the remainder of the patient's life. In the women who developed late manifestations of syphilis, the visceral involvement, especially cardiovascular, was most often seen. Tertiary lesion of the bones, skin and nervous system were rare. The Wassermann reaction in these cases of latent syphilis was very prone to marked vacillation without treatment, either a negative or positive reaction during pregnancy being changed to the opposite after delivery.

Bronchial Moniliosis.—STEINFELT (*Jour. Am. Med. Assn.*, 1924, 72, 83) describes 15 patients with bronchial asthma and chronic bronchitis in whom an allergic state with regard to the usual pollen and epidermal food proteins was not demonstrable, all of whom showed an interesting bronchomycosis with the appearance of monilia in the sputa. All of these patients showed eosinophilia. The ages varied from twenty-five to sixty years. Seven were in men; 8 were in women. In all the process began in Philadelphia. Clinically these were characteristic instances of bronchial asthma associated with general bronchitis and paroxysms of expiratory dyspnea with audible wheezing, and, in the active stages, sonorous and sibilant rales generally on both sides. In some there were also subcrepitant rales and a picture which, at times, suggested bronchiectases or tuberculous changes. But there was never dulness on percussion and all cases cleared up under proper treatment. In all of these cases there were found in the sputa, white, chalk-like particles or indeed actual islands composed of colonies of yeasts. Sometimes they were amber colored. Under the high-power objective they consisted of globular fat-like spores and sometimes in severe cases, developed hyphæ and mycelia. Cultures of these particles yielded yeasts of the genera *Monilia* *cryptococcus* and *endomyces*. Suspensions of cultures injected into guinea-pigs intraperitoneally or intratracheally produced eosinophilia in the exudates and in the blood, and eosinophilia were always present in the human beings. While insisting upon the careful attention to any abnormalities in nasal passages, tonsils and sinuses, it is the author's belief that striking benefit resulted from the employment of iodides in doses of from 2 to 4 gm. per day (gr. xxx to cxx). Moreover he feels that improvement was facilitated by the injection of vaccines prepared according to the method of Michel.

Hyperglycemia as an Etiological Factor in Certain Dermatoses.—MCGLOSSON (*Arch. Dermat. and Syph.*, 1923, 8, 665) has studied a large number of chronic dermatoses from the standpoint of the sugar content of the blood. Most of the conditions could be grouped under the head-

ing of "eczema," using this term generically. In but few of the cases was there a glycosuria, but most showed a blood sugar content of higher than 0.11 per cent, which was taken as the upper limit of normal. The usual treatment was used, including roentgen-ray, but in addition a restricted carbohydrate diet. The improvement was so much more striking when carbohydrate was restricted that the author concluded that a hyperglycemia was at least one of the factors in this class of dermatoses. This conclusion was strengthened by the fact that there would often be a return of the dermatitis if carbohydrate was added too rapidly to the diet. A number of extremely interesting cases are cited.

Treatment of Neurosyphilis.—SOLOMON (*Jour. Am. Med. Assn.*, 1923, 81, 1743) describes the anatomy of the central nervous system in relation to syphilitic infection and makes a worth-while differentiation between parenchymatous syphilis, such as paresis or tabes, and meningo-vascular syphilis. He points out how the central nervous system is separated and shut off to a large extent from substances in the general circulation. In general, it was found that meningo-vascular syphilis reacts the more favorably to treatment, and this confirms previous work. Some cases of what were apparently paresis, however, did very well on the ordinary treatment with arsphenamine, mercury, and iodides. The author advocates introducing the medicament as near the site of pathological change as possible, using the lumbar, cisternal, or ventricular routes, as indicated. The immunity of the patient is a factor, and mention is made of the theory of increasing the immunity by inducing febrile reactions, such as by injection of foreign protein, or by inoculation with malaria. Solomon mentions tryparsamide in passing. Further reports of the use of this drug in paresis will be interesting.

On Bronchial Breathing.—MARTINI and MUELLER (*Deutsch. Arch. f. klin. Med.*, 1923, 143, 129) making a new contribution to the interesting series of studies on physical diagnosis which have come from the latter's clinic. By ingenious methods of analysis of the vibrations induced in the air content of various systems of tubes analogous to bronchi and in bronchi in the human body they come to the conclusion that the point of origin of the sonorous vibrations characteristic of bronchial breathing lies in tubes of a relatively large lumen—those with a diameter of from 4 mm. upward. To convey these sounds to the periphery so that they may be audible on auscultation of the chest there must be a continuous area of solidified tissue reaching from the periphery to a depth of from 3 to 5 cm., for such is the usual distance of such bronchi from the periphery. But a small layer of normal lung tissue masks tubular respiration. Only near the spine, in the interscapular space may areas of solid tissue from 1 to 2 cm. deep suffice to convey bronchial respiration to the ear. The conception that bronchial respiration is characteristic of solidified lung tissue and is produced in the finest bronchi with firm walls has no foundation.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Retroperitoneal Perirenal Lipoma.—JOHNSON (*Boston Med. and Surg. Jour.*, 1923, 189, 907) says that lipomata are probably the most frequent growths in retroperitoneal sites. - Owing to slow growth and lack of characteristic symptoms they attain great size before their discovery. The most common sites are the perirenal fat and the fat at the root of the mesentery. These growths are more frequent in females than in males, and between the ages of forty and fifty years. They may be pure lipomata, but rather more than half are of the mixed variety. They may undergo sarcomatous degeneration. Emaciation at times becomes marked—the condition being inoperable in some cases. Mortality is between 15 and 20 per cent.

Subperiosteal Resection of Long Bones in Osteomyelitis.—BEYE (*Surg., Gynec. and Obst.*, 1923, 37, 732) states that it is fundamentally unsound to do a subperiosteal resection of the shaft of a long bone for osteomyelitis. In performing such an operation bone may be sacrificed, which if properly drained would not only be viable but play an important part in the restitution of the diseased shaft. Regeneration of bone from the periosteum remaining after subperiosteal resection may be limited and stop far short of a functional end-result. Deformities are likely to follow such an operation with resultant functional disability. The radical removal of diseased bone by this procedure does not necessarily mean that infection has been eliminated.

Arthroplasty.—GROVES (*Brit. Jour. Surg.*, 1923, 11, 234) says that arthroplasty should be defined as an operative procedure upon an ankylosed joint, which has the object of restoring mobility. The pseudoarthrosis which sometimes results from a simple fracture proves that a new joint can be formed including fitting articular ends, capsule and synovia, without any plastic operation. Clinical evidence as to the result of arthroplasty is conflicting. There is ample evidence that operative mobilization of the elbow-joint is usually followed by greatly improved function, while arthroplasties for hip and knee often lead to disappointment or failure. The condition most favorable for arthroplasty is bony ankylosis due to trauma or pyemia which has long been cured. Certain cases of tubercle and osteoarthritis also give good results. The essential act in arthroplasty is to make a gap between the articular ends and to maintain this gap while healing takes place. Shaping and covering the articular ends is useful, but not essential. Continuous traction on the articulation and early voluntary movements

are the essentials of after-treatment. In the elbow the indications include all cases of bony ankylosis free from active infection, except those in which a strong useful arm is present in a laboring man. The best operation for the elbow is to preserve the whole width of the humeral condyles and to cover this bone with a free flap of fascia lata. In the hip, for simple ankylosis, an osteotomy of the neck of the femur with interposition of a flap taken from the trochanter or from the capsule. For massive hypertrophic ankylosis a subtrochanteric osteotomy, with the interposition of a fascial flap, forming a saddle-shaped joint. For osteoarthritis, excision of the head of the femur is indicated. In the knee, the importance of stability and painlessness makes any mobilizing operation unjustifiable if the joint is fixed in a good position. It is only in the cases of ankylosis of both knees that arthroplasty is to be considered. The use of free fascia to cover the lower end of the femur, the preservation of the lateral ligaments and the use of a jointed knee cage for some months after operation are the special points on which stress must be laid. If lateral mobility persists, then lateral and crucial ligaments must be reinforced by a second operation.

Bilharziasis of the Ureter.—BRAHIM (*Lancet*, 1923, 205, 1184) says that bilharziasis of the ureter exists, and may be the only or the most prominent manifestation of the disease, which is usually bilateral, though more advanced on one side than on the other. The disease is very chronic and the stages merge one into the other. The disease ends in the formation of fibrous tissue which replaces the normal coats of the ureter. This leads to contractions and narrowing or even complete obliteration of the lumen of the lower part of the ureter. Secondary to this, the upper part of the ureter and pelvis of the kidney become dilated. Ascending infection is rare and is mostly a complication of bilharziasis of the bladder. If neglected, the disease is very fatal, ending in death from uremia and rarely from septicemia.

Experimental Cord Crushes.—MCVEIGH (*Arch. Surg.*, 1923, 7, 573) states that edema and hemorrhage are factors to be dealt with in partial lesions of the cord. Release of pressure seems to have no effect in checking edema formation. In complete lesions of the cord, the cord at the site of the lesion is reduced to a pulp and blood mixture, and the ends of the cord separate for a short interval. The pulp is forced into segments above and below the lesion, and causes an increased intrapial pressure, which is released in one of two ways; by rupture of pia, or the tracking of pulp up and down the cord until pressure is relieved. The area of the cord involved in complete lesions is the area of least resistance, located in the ventral part of the dorsal white columns and that part of the central gray matter dorsal to the cerebral canal.

Cardiorrhaphy in Acute Injuries.—SMITH (*Ann. Surg.*, 1923, 78, 696) says that cardiorrhaphy is a comparatively recent advance in surgery. The human heart is very tolerant of manipulation. This fact has been repeatedly demonstrated, especially in connection with foreign body extractions during and since the World War. Surgical pneumothorax is remarkably well tolerated. The symptomatology of heart injuries varies widely and as a consequence the diagnosis of this

condition is often very difficult. Therefore exploratory operations are justifiable. Transpleural thoracotomy under general anesthesia is probably the procedure best suited to the average case of this type. Drainage in this case can be accomplished best through the medium of a simple valve-tube drain through the chest wall.

Surgery of Seminal Vesicles.—MORRISEY and SMITH (*Surg., Gynec. and Obst.*, 1922, 37, 480) says that inflammation of the seminal vesicles is a well-defined and recognized surgical condition occurring usually as a sequel to previous infections of the genito-urinary tract. It is a condition that can be relieved surgically either by drainage or extirpation of the vesicles. Operation on the vesicles combine all difficulties of perineal prostatic surgery and a well-established technic must be employed properly to meet indications for operation. Procedures aiming to drain vesicles through skin incisions and punctures are ineffective, and results reported following inaccurate technic cannot be taken into account. Figures and results in a large series of cases with bacteriological findings and improvement noted in a large proportion of cases justify the establishment of the operation and a more frequent use as a surgical procedure in selected cases.

Tuberculous Enterocolitis.—LEMON (*Minn. Med.*, 1923, 6, 572) says that the fundamental functions of the body in tuberculosis are apparently affected by the disease itself, and not influenced particularly by the site or area involved. Obstruction or stenosis and perforation are more common in tuberculous enterocolitis than has been believed. There are no characteristic symptoms which will definitely locate in any special area of the bowel. The surgical and necropsy evidence of tuberculous enterocolitis is almost invariably more widespread than the clinician could anticipate.

The Relation of the Bowel to B. Coli Kidney Infections.—DAVID and MCGILL (*Jour. Urol.*, 1923, 10, 233) say that in control dogs with normal intestines the mesenteric glands contain bacteria in over 50 per cent and contain *B. coli* in 33 per cent of the glands examined. These facts speak conclusively for the passage of organisms from the normal bowel to the mesenteric glands. Injection of large amounts of actively growing *B. coli* into the normal gastro-intestinal tract of dogs was associated with the presence of *B. coli* or *B. coli*-like organism in the urinary tract in 3 of 11 dogs. It is probable that these organisms reached the urinary tract by way of the blood stream. No evidence was forthcoming that organisms reaching the mesenteric glands from the bowel tended to involve the urinary stream by way of the lymphatics. The significant of the passage of intestinal organisms through normal as well as a pathological bowel wall to the mesenteric glands cannot be overlooked. While it is undoubtedly true that these organisms reach the blood stream in but relatively small numbers and incessantly, it is nevertheless possible that increased virulence of the organisms, lowered resistance of the host as well as actual lesions of the bowel wall would greatly increase this number of organisms reaching the blood stream.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK.

Principle Viewpoints on the Question of Protein Therapy.—SCHMIDT (*Therap. d. Gegenw.*, 1923, 64, 337) gives the practical indications for protein therapy, and reminds the reader that no real difference exists between the results obtained by injections of blood, serum, vaccines, milk or tuberculin. In general the use of proteins is comparable to hydrotherapy in its non-specificity, both measures affecting the whole system in a general way. The general principles of protein therapy have been derived from empirical experience, and though various substances may apparently give the same clinical macro- and microscopical results, nevertheless the chemico-biological results may be different. He bases the indications for protein therapy on two facts: (1) Injection of protein substances causes increased bio-chemical activity of which an increase in body temperature is only one indication; (2) injection of protein substances increases the bio-chemical reactions at a point in the body where some focus of low-grade infection already exists—from which he infers that two results may follow: (1) In chronic inflammatory conditions a continuation of the inflammation may lead to a diminution of the same; or a lighting up of a chronic stationary condition may result in its complete cessation; (2) focal reactions are double phased under the action of protein substances, that is, with an increase of the inflammation, fever, etc., in the negative phase there follows a positive phase shown by the diminution of the temperature and subsidence of the inflammation, and the patient feels well during this positive phase as he felt ill during the negative phase. The particular indications for protein therapy are formulated by the author as follows: (1) Chronic, fixed and focal exogenous infections, *e. g.*, tuberculosis of bones and peritoneum; gonorrheal rheumatism and epididymitis; chronic eye, ear and joint processes; (2) chronic indolent endogenous aseptic inflammations, and abnormal metabolic conditions attending them, *e. g.*, neuralgia and arthralgia with disturbed uric acid metabolism; also constitutional diseases such as late rickets and osteomalacia. Bronchial asthma and cases of high blood-pressure are often influenced for good because of their close relation to abnormal metabolism. Combining the protein injections with other therapeutic measures may increase the effectiveness of the the latter, *e. g.*, milk injections with adrenalin in osteomalacia, neuralgia, chronic arthritis and late rickets, and with thyroid tablets in obesity; (3) chronic febrile states can often be cured as a result of the double-phased reactions of protein therapy; (4) hemorrhage. In particular milk injections have been proved to create an increased coagulating power in the blood. In severe hemorrhage (typhoid and duodenal ulcer) protein therapy is often indicated. The following technic is advised by the writer: Whole milk sterilized for ten minutes in the

water bath is used as the protein substance in this form of treatment. This combines the albumens of the milk with the dead bacteria always present, of which the streptococci and bacillus coli appear to be the principle agents in producing a reaction. The secret of the value of protein therapy lies in the focal reaction. The dose is given intramuscularly and varies between 0.5 and 5 cc. Whenever high fevers may be caused as in tuberculosis, lues, pernicious anemia, and leukemia it is wise to begin with small doses of 0.5 cc. The injections are given every two or three days and an amount used which will give a moderate general and focal reaction. The length for such a course of treatment is about four weeks.

Experiences with Atophanyl.—ZIMMERMANN (*Therap. d. Gegenw.*, 1923, 64, 390) reports successful results in the treatment of acute rheumatism, neuralgia, and chronic rheumatism with atophanyl (E. Schering) which is a solution of the sodium salts of salicylic acid and atophan for intravenous or intramuscular injection. The ampules contain 0.5 gm. of each salt dissolved in 5 cc of liquid. This preparation can be given to patients with kidney or liver trouble without damage, but should not be used in cases of pneumonia or pericarditis. Five cc of atophanyl are given once each day for three days, and the results obtained were more satisfactory than those obtained by the use of sodium salicylate or of atophan by mouth.

The Treatment of Pyelitis.—HOHLWEG (*München. med. Wchnschr.*, 1923, 42, 1297) concludes from his extensive experience in the treatment of pyelitis and cystitis that the most important agent is local irrigation of the bladder and kidney pelvis with 0.5 to 1 per cent solution of silver nitrate. He irrigates the kidney pelvis two to four times a week using the 0.5 per cent solution, and the 1 per cent solution for irrigation of the bladder. Because of the frequency of recurrence he considers no case cured unless the urine is bacteria-free. Instead of employing urotropin, salicylic acid and other urinary antiseptics he uses intravenous injections of 20 cc of a 0.5 per cent solution of argoflavin daily for eight to nine days. One third of the cases of pyelitis and cystitis due to the colon bacillus were cured with the intravenous injections alone. The remaining two-thirds required in addition the use of the irrigations of silver nitrate. He concludes that the ideal treatment of infections of the bladder and of the pelvis of the kidney is a combination of local irrigation with silver nitrate and intravenous injections of argoflavin.

The Rationale of Parathyroid Therapy.—VINES (*Brit. Med. Jour.*, November, 1923, p. 854) calls attention to the similarity of the signs of acute infection (fever tachycardia, sweating, shivering, increased metabolism, hyperglycemia, and loss of calcium from the body) to overaction of the thyroid gland. Overaction of the thyroid submerges the regulating action of the parathyroid as is shown by loss of calcium. Continuation of these symptoms in chronic infections leads to a pathological and new level in the sympathetic-parasympathetic balance, and an improvement in chronic infections may be obtained by restoring the normal balance by the administration of parathyroid substance or to a less degree by the administration of calcium salts.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

The Development of the Topography of the Larynx, Trachea and Lungs in the Fetus, New-born Infant and Child.—NOBACK (*Am. Jour. Dis. Child.*, 1923, 26, 515) says that the descent of the respiratory system in relation to the vertebral column during childhood is not peculiar to that period in the development of the individual. It is merely a stage in a process in which manifestations begin in early fetal life and which continue to operate during infancy, childhood and maturity. During fetal life the topography of the epiglottis shows practically no change. It remains quite constantly opposite the first cervical vertebra. This level persists through infancy and childhood until puberty, when the adult relationship is attained so that it lies opposite the third cervical vertebra. The inferior margin of the cricoid cartilage and the lower limit of the larynx descends during the course of prenatal life from opposite the third to opposite the fourth cervical vertebra, a distance of one vertebra and one intravertebral disk. During infancy this relationship remains constant, but during later childhood another descent to the level of the sixth cervical vertebra takes place, a drop of two vertebrae and one disk. With the reaching of maturity the inferior limit of the larynx is opposite the seventh cervical vertebra. The bifurcation of the trachea undergoes a descent from opposite the third to opposite the fourth thoracic vertebra, a descent of one vertebra and one disk. This relationship is maintained during infancy, but in childhood another descent takes place, and by puberty the bifurcation is opposite an area between the fourth and fifth thoracic vertebra. This level is maintained through adult life. The apices of the lungs remain at practically the same level as the suprasternal notch throughout the course of fetal life. The upper poles of the lungs in relation to the vertebral column undergo a slight descent during prenatal life from a level opposite the seventh cervical or first thoracic vertebra to the upper margin of the second thoracic vertebra. This level is apparently maintained throughout the course of postnatal life. The inferior margin of the lungs during fetal life undergo a descent from between the ninth and tenth to opposite the tenth to twelfth vertebrae. The latter level which is present at birth, coincides quite closely to the levels given in the standard text-books for adults, thus indicating that the postnatal growth in length of the lungs is closely correlated with the increase in the length of the thorax. The lobes of the left lung in the human fetus do not vary much from the condition in the adult. The lobes of the right lung are markedly different from the lobes in the adult. The depth of the cardiac notch during prenatal life is very variable. There is a general increase in depth with increase in body length.

The Acidity of the Gastric Contents of Infants.—MARRIOTT and DAVIDSON (*Am. Jour. Dis. Child.*, 1923, 26, 542) point out that the acidity of the gastric contents of a group of normal breast-fed infants at the height of digestion averaged pH 3.75. The acid normally present is sufficient to perform a number of important functions. Any considerable decrease in the amount of acid is likely to be associated with digestive disturbances. The acidity of the gastric contents of infants suffering from infections or nutritional disturbances is distinctly lower than that of normal infants. Sweet cow's milk, by reason of its high buffer value, is capable of neutralizing a considerable portion of the acid of the gastric juice. This is one important reason why large amounts of sweet cow's milk cannot be well tolerated by infants. Milk containing from 0.5 to 0.7 per cent of lactic acid does not neutralize the acid of the gastric contents to any greater extent than does breast milk. When such milk is fed undiluted to infants, the acidity of the gastric contents approximates that of normal breast-fed infants. It is probable for this reason that infants are able to tolerate large amounts of lactic acid milk. The observations show that the gain in weight was distinctly greater during periods of feeding when one of the lactic acid containing milks was used, than during the sweet milk periods. There was a more striking gain in weight and a lesser incidence of gastro-intestinal disturbances among this group of infants than among the sweet milk group.

Reasons for the Failure to Obtain Relief after Tonsil and Adenoid Operations.—GOLDBERGER (*Arch. Pediat.*, 1923, 40, 767) claims that sinusitis is a disease common in children and may occur at any age. Children, whose catarrhal conditions of the upper respiratory tract do not subside after tonsillectomy and adenoidectomy, suffer in all probability from accessory nasal sinus disease. The children who are operated upon for the return of adenoid growth are probably victims of sinusitis. The antrum is the most frequently involved sinus. Two forms, the catarrhal and the purulent, are met with. Children should not be discharged as cured after upper respiratory infections such as cold, grippe, and the like, and after the acute eruptive fevers such as measles and scarlet fever particularly, until all signs pointing toward sinus involvement have subsided. Children should return at periodic intervals after operations on the upper respiratory structures to ascertain the condition of the sinuses. A hint as to the presence or the absence of sinus involvement is often obtained while the patient is under ether. Symptoms are usually constant in typical cases. Complications such as osteomyelitis, abscess of the orbit and of the brain, and meningitis are not uncommon. Diagnosis rests upon the history of previous events, roentgenograms, transillumination, and exploratory puncture. Treatment is usually conservative. Most men favor suction. Operations should be done only after all other procedures have failed.

Syphilis as a Factor in the Etiology of Mental Deficiency.—WEISS and IZGUR (*Jour. Am. Med. Assn.*, 1924, 82, 12) tested 1794 sera from 1633 patients. Of these, 41 or 2.5 per cent were positive, and 44, or 2.7 per cent, were doubtful. If every case presenting from one

to four plus reactions on the cholesterinized antigens is considered a case of syphilis the total incidence of syphilis based on the Wassermann reaction would be 5.2 per cent. One hundred and twenty or 15.5 per cent of the patients examined clinically, presented at least one of the so-called stigmata. Of these only 13 presented more than one so-called stigma, 107 presented only one. Of those that presented only one stigma, in 85 it was unilateral or bilateral epitrochlear enlargement. In only 1 case was there the typical picture of Hutchinsonian teeth, saddle-back nose, rhagades, evidences of a past interstitial keratitis. This study was undertaken for the purpose of determining the frequency of syphilis in mental defectives. Less than 3 per cent of the defectives were syphilitic by serological test. Clinical examination revealed 15.5 per cent of the defectives with one or more of the so-called stigmata. They conclude that syphilis is uncommon in mental defectives, and that it is less common than in the general population. They question whether there is any etiological relationship whatever between syphilis and mental deficiency. They claim that if syphilis was a cause of mental deficiency, it should occur more frequently in mentally deficient children than in mentally normal children.

Diphtheria Carriers among School Population of Baltimore.—DOULL and FALES (*Am. Jour. Hyg.*, 1923, 3, 604) made combined nose and throat cultures from 7790 children, selected at random from schools situated in the northeastern section of Baltimore. There were 409 or 5.25 per cent carriers of morphological and 136 or 1.75 per cent of virulent diphtheria carriers. The rate of carrier infection varied greatly at different seasons of the year. The incidence of carriers of virulent diphtheria organisms was 3.29 per cent in November and December and 1.49 per cent in February and March, and 0.87 per cent in May and June. This variation at different seasons in carrier incidence coincides with the seasonal variation observed in diphtheria morbidity. There is a remarkable constancy at the different seasons of the year in the percentage of cultures containing morphological diphtheria bacilli which on further test were found to be virulent. These percentages were 30.45, 29.59 and 26.09 respectively in three surveys. The seasonal variation in carrier incidence was generally consistent in individual schools. The rate of carrier infection was not significantly different in the two sexes for the age period covered in this study. There was a slight but not significantly lower carrier rate among colored children than among white children. A slightly but consistently higher incidence of carrier infection was found in the younger than in the older children. Taking in consideration all of the schools surveyed, definitely but not greatly higher rates of carrier infection were found among those children who had enlarged and diseased tonsils than among those with normal tonsils. There was no noticeable difference in the carrier incidence between those having had their tonsils removed and those with normal throats. There was significant difference between those children who had histories of previous attacks of diphtheria and those with no such history in considering carrier incidence.

The Effect of Light on Organism.—CRAMER and DREW (*Brit. Jour. Exper. Path.*, 1923, 4, 271) studied the physiological action of light on

ordinary mercury vapor bulb on the animal organism. Rats born and kept in darkness frequently show a diminution in the number of blood platelets as compared with rats kept on the same vitamin-poor diet in a well lighted room. This thrombopenia is sometimes associated with a definite anemia. Exposure of such animals to a mercury vapor lamp increases the number of blood platelets to normal, and if an anemia is present, it increases the number of red cells. Rats kept in darkness do not exhibit intestinal lesions such as are found in vitamin-A deficiency nor do they develop the bacteria infections, such as xerophthalmia, and septic lymph glands characteristic of that deficiency. They do develop these conditions sooner when placed on a deficient vitamin-A diet, than rats kept in a well-lighted room. Rats kept on a vitamin-A-free diet develop a progressive thrombopenia and atrophy of the intestinal mucosa. Exposure to a mercury vapor lamp, if applied from the beginning of the deprivation of this vitamin, delays the thrombopenia. If applied after a thrombopenia has set in, it will increase the number of platelets. Such exposures do not affect the eventual onset of the atrophy of the intestinal mucosa. Therefore it would seem that the light stimulates the formation of blood platelets. This explains the partial antagonism between vitamin-A-deficiency and exposure to light. Light is not an essential to the formation of blood platelets. In the absence of light, sufficient vitamin-A will prevent the thrombopenia.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Bismuth Salts in the Treatment of Syphilis.—Further favorable reports on the use of bismuth in the treatment of syphilis have continued to appear. KLAUDER (*Arch. Dermat. and Syph.*, 1923, 7, 721) summarizes current observations. The dosage of bismuth preparations ranges from 0.1 to 0.2 gm., the injections being given intramuscularly every second to fourth day. Intravenous use is absolutely contraindicated. Approximately from 1 to 2.5 gm. is probably the average total tolerated dose in one month. The good effects persist for some time after the cessation of administration. Fifty per cent bismuth inunctions in human syphilis exert a feeble spirocheticidal action. So far as spirillicidal action is concerned, bismuth can be placed about midway between mercury and arsphenamine. HOPKINS (*Arch. Dermat. and Syph.*, 1923, 7, 745) finds sodium and potassium tartrobismuthate more effective than mercury salicylate and probably approximately equal to neoarsphenamine. McCafferty (*Arch. Dermat. and Syph.*, 1923, 8, 469), with observations on 600 injections, rates the efficiency of bismuth in primary and secondary syphilis as equal to that of arsphenamine, though slower both clinically and

serologically. He calls special attention to its efficiency in Wassermann-fast syphilis and in those who have an idiosyncrasy for arsphenamine. Stomatitis and pigmentation of the mucous membranes are negative factors in treatment, in his estimation. He noted favorable effects on the symptoms of neurosyphilis. The dosage for children is 0.01 gm. per kilogram of body weight, which is proportionately larger than for adults (Cajal and Spierer).

Treatment of Pemphigus.—The intractable character of chronic pemphigus and the usual fatal outcome make any contribution to the treatment of this disease of interest. R. H. and W. D. DAVIS (*Arch. Dermat. and Syph.*, 1923, 8, 627) report a method of treatment based upon the familiar use of arsenic with the addition of coagulen. The treatment consists of intravenous injections of 1 gr. of iron cacodylate three times a week and 1.5 cc coagulen subcutaneously. The preparations may be used simultaneously or in alternation, and should be continued over a considerable period, with rest intervals of one month in every three or four. Of 7 cases reported as treated by this method, 1 recovered completely after eleven months; 2 recovered in from three to six weeks; 1 patient was almost well; 1 improving, and there had been 1 death up to the time of reporting. The treatment seemed to be the most effective in acute rapidly progressive cases. In the discussion which followed the presentation of this paper, and in the paper itself, attention was called to the remissions well known to occur in pemphigus, some of which may be very prolonged and give the impression of cure. Ormsby gave it, as his belief, that pemphigus is always fatal, although some cases run a protracted course. He alluded to the value of blood transfusions in occasional instances, reporting 1 case in which six were given, with remarkable improvement. On the other hand, Schamberg has seen no favorable effects from this procedure. The general trend of the discussion certainly indicated the profound uncertainty surrounding the treatment of this disease and the fact that even apparent clinical cures do not necessarily mean a permanent result. Any method of treatment, however, deserves consideration and trial under the circumstances.

Thymus Irradiation in Psoriatics.—GAWALOWSKI (*Acta dermat.-ven.*, 1923, 4, 105) discusses his experience with the irradiation of the thymus gland in adults for the treatment of psoriasis. The rationale of the procedure is based on Samberger's and Brock's observations, which led them to maintain that psoriasis is a disorder of keratization which is controllable to some extent through the hormone of the thymus gland. The author discusses in some detail the roentgenological technic of reaching the glandular tissue behind the sternum, since much depends upon accuracy of dosage. In 82 treated cases, 17 per cent were cleared up, 48.8 per cent improved, no results were obtained in 6.1 per cent, 2.4 per cent were made worse and 25.7 per cent disappeared from observation. This gives 65.8 per cent benefited, as compared with Brock's 66 per cent. The dosage employed was higher than Brock's, and only two treatments were required to produce the best results. The interval between treatments was six weeks. The 9 patients who were made worse or received no benefit were later

cleared up with Byla's "thymosine." Twenty non-psoriatics were likewise treated. Pigmentary disturbance in 1 case, marked sweating, increased capillary irritability and marked itching were occasionally noted. The results in psoriasis justify the method in the author's opinion.

Arsenical Melanosis and Argyria of the Skin and Mucous Membranes after Silver and Neoarsphenamine.—KOGOR (*Acta dermat.-ven.*, 1923, 4, 94) describes what appears to be the first authentic instance of argyria following the use of silver arsphenamine. The patient was a young woman, who, after twelve injections of silver arsphenamine and twelve injections of neoarsphenamine, developed a dirty-gray pigmentation of the entire skin and all visible mucous membranes. The author studied elaborately the various differential possibilities and the histological characteristics of the lesion, reaching the conclusion that the pigmentation combined the known characteristics of arsenic and silver pigmentations of the skin. The literature of the various pigmentary disturbances, including melanoses ascribable to the arsphenamine, is elaborately cited, with a bibliography of sixty-eight titles.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

An Unusual Accident during Delivery at Term.—MARTIN and BRINKLEY (*Virginia Med. Month.*, October, 1923, p. 457) describe the case of a multipara in labor supposed to have the child in breech presentation. Labor proceeded slowly and the physician returned some hours after making an examination intending to give chloroform and deliver the child. On a second examination, the face presentation was recognized. When the cervix was fully dilated the patient was given chloroform and pituitrin; this was followed by a very severe uterine contraction with several slight pains during the next thirty or forty minutes. There was a moderate flow of dark blood from the vagina. The head did not descend and the physician prepared to perform version. On introducing his hand it entered the abdomen; version was quickly performed and a dead child delivered. The placenta was readily removed. On further examination the vaginal vault was almost completely torn away from the cervix and packing of sterile gauze was introduced and the patient sent to a hospital. Under anesthesia the abdomen was opened, when it was found that the uterus had been torn away from its vaginal attachments almost completely. The broad ligaments were lacerated almost up to the pelvic brim on either side. On the right side the tear extended through the vaginal wall practically to the vulva. The uterus, left

tube and ovary were removed. The torn fascias were brought together, the vessels tied and a drain inserted. The patient made a somewhat tedious recovery. There was drainage through the vagina and some sloughing tissue came away. About a month after operation the patient left the hospital and was found, when examined subsequently, to be in good condition. The combination of chloroform and pituitrin seems an unusual one. Apparently the purpose was to remove pain and stimulate uterine contraction. The result was what may be expected in cases of abnormal presentations and complicated labor, when pituitrin is given. No more dangerous procedure could be employed.

Liniae Albicantes in Varying Degree in Pregnancy.—KERMAUNER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 64, 125) calls attention to the fact that the occurrence of this phenomenon in pregnancy has been supposed to be of a purely physical nature. Sellheim has called attention to this occurrence as a biological element. The writer has studied the subject from this point. It has commonly been supposed that this evidence of distention of the skin of the abdomen is most marked in young primiparæ indicating the increased tension upon the tissues. This, the writer does not accept. He believes that peculiarities in the shape of the mother's body predispose to this occurrence. He has found this distention of the skin most abundant on the abdomen beneath the umbilicus, extending to the pubes, on the inner aspect of the thighs, the outer portion of the hips extending to the mid-line in cases where the entire abdominal wall has been firm, smooth and moderately fat. Where the tissues were relaxed, this condition developed a hand's breadth above the umbilicus and but little in the region of the hips. In some cases this was seen four fingers' breadth above the pubes, extending across the abdomen, the remainder of the abdomen remaining free. At other times the upper portion of the thighs and hips, and even the back showed this condition. The writer believes that edema of the skin has nothing to do with the formation of these so-called "stripes." Furthermore, he does not consider that distention alone of the tissues accounts for their occurrence. He has seen a similar condition in the bodies of men where the abdomen has grown fat very rapidly. He has never seen it where ascites or tumor was present. He is convinced that the occurrence of this phenomenon depends upon conditions in the connective tissue in the deep fat of the abdominal wall. Pregnancy, naturally, supplies the conditions favorable for increased nutrition and for increased contraction and relaxation of abdominal muscles. That it is not the pressure of the enlarged uterus is shown from the fact that in early pregnancy, when the uterus is still deep in the pelvis, patients complain of increased pressure and a sensation of weight in the abdominal walls. Multiparæ often feel this more acutely than primiparæ. Distention of the bowel may have something to do with this, but the increased deposit of fat, called by Bauer "lipophilie," is the essential element. In cases where this process goes on in the breasts the stripes may also develop. The writer cites the case of a young woman, aged twenty years, who became fat very suddenly. In six months the condition had increased so greatly that ascites and edema were present and the

appearance of the patient, when compared with a photograph taken four years previously, would not have permitted her recognition as the same person. These stripes appeared over the whole body with the exception of the face. One may the better understand this condition by considering the connective tissue of the skin as divided into practically two layers, one of which is superficial, the other deeper. It is in the deeper layer that this phenomenon develops. The writer considers the condition known as dystrophia adiposogenitalis, as allied to that under discussion. A lack of function in the pituitary body is thought to be the cause, and if this persists after delivery the abdominal fat condition may greatly impair the appearance of the patient. One occasionally sees cases in which the elasticity of the skin is excessive. In these patients the eyelids, the tissues about the neck and about the ears may hang in folds. Very badly nourished children may also show these symptoms. In multiparous women, whose tissues are greatly relaxed and wasted the same is seen. Myxedema must not be confused with this condition. In myxedema there are no stripes formed, and the administration of glandular extracts clears up the condition. It can also be differentiated from edema of the skin. It cannot be overlooked that in pregnancy all tissues become unusually elastic and lose their tone readily. To this is added disturbances of function in secretory glands, and when these conditions are considered it is not strange that such phenomena should appear.

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,
DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,
PHILADELPHIA.

The Toxic Action of Tobacco and Alcohol upon the Eye.—SATTLER (*Klin. Monatsbl. f. Augen*, 1922, 60, 526) reports that visual disturbances from tobacco and alcohol have increased six-fold at the Konigsberg University Eye Clinic from 1913 to 1921. Inquiry as to the cause of such increase among 47 patients showed that about one-half had been smoking or chewing not ordinary tobacco, but self-grown, simply dried; the latter contains about twice the amount of nicotine as the properly prepared tobacco of commerce; chemical examination showed, moreover, that whereas only 15 per cent of nicotine went over in commercial tobacco, 27 per cent did so in the simply dried form. A coöperating cause is unhygienic way of smoking: short dirty pipes, inhalation of the smoke into the lungs. The fact that over one-third of the patients were imbibers of distilled spirits (0.1 to 0.25 liter daily) makes it prob-

able that the methyl alcohol content of 2 per cent contained therein exerted a toxic effect upon the eye; each daily dose of 0.5 liter contains 10 gm. of methyl alcohol (minimum toxic dose for the eye $\frac{8}{10}$ gr.) which in consequence of protracted oxidation and excretion (methyl alcohol three to five days, ethyl alcohol only twenty hours) may exert a deleterious effect upon the eye through cumulative effect. Under-nourishment is a predisposing cause of lessened resistance to poisons. Examination of the visual field for white and colors showed in 21 cases different zones of saturation of the so-called central scotoma; the point of greatest saturation in about one-half the cases did not involve the point of fixation, but a region between this and the blind spot, generally in the mid-point, but occasionally nearer one or the other extremity; in the remaining half of the cases saturation was limited to the point of fixation; in 3 cases the scotoma lay above or below this point; in none did the defect extend into the periphery. During convalescence the scotoma gradually receded to the point of fixation or to the blind spot; a larger scotoma for red in 2 cases vanished before that for blue; all the cases were recent. The above clinical determinations of the scotomata so variable in form, extent and density are explicable by the anatomical findings of the variable areas of degeneration observed to occur in the optic nerve.

Glaucoma and Syphilis.—CARLOTTI (*Clin. Ophthalm.*, 1923, 12, 428) observes that the role played by syphilis in the causation of the different forms of glaucoma has been noted by a number of authors. It is, however, remarkable that in the some 50 publications devoted annually to glaucoma, lues and its therapeutic indications plays so little a role. Thus Elliott in his very complete review, does not allude to syphilis. Gama Pinto in his article for the Encyclopedia remarks "that syphilis has been mentioned among the causes of glaucoma; Connor, Rechev, Pflueger and Samelsohn claim to have observed cases of glaucoma which were not cured by surgical intervention but yielded to antisiphilitic treatment. Morax also admits that glaucoma may be a secondary consequence of specific disease." The author reports 26 cases of glaucoma which go to prove that treponemic infection may give rise to all varieties of glaucoma, and that such ocular localization is subject to the same rules from the therapeutic point of view as other manifestations of syphilis. Medical treatment should be prompt and prudent in two of the cases cited, injections of cyanide were followed by apparent aggravation. When the glaucomatous lesions are advanced, surgery takes the place of medical therapeutics.

Final Results of Sclerecto-iridectomy in the Treatment of Chronic Glaucoma.—LAGRANGE and BARON (*Arch. d'ophth.*, 1923, 40, 15), the former of whom introduced subconjunctival scleral resection in 1905 for the purpose of effecting permanent fistulization, sum up results obtained by this method, in 49 patients operated upon between 1912 and 1921 and followed from one to ten years; the results show that operative success was maintained in 82 per cent of the cases, as regards visual acuity, if the development of senile cataract subsequently is disregarded, and 73.1 per cent if the latter is considered a cause of impaired vision. The same series shows that the intraocular tension remained normal

in 8 per cent, and if hypotonia can be regarded as favorable, in 87.5 per cent. There was never any infection, primary or secondary; since the scleral orifice was recovered by a thick layer of mucous membrane; neither was there hypotonia from wounding of the ciliary body because the excision is purely scleral, about 3 mm. in length, and does not exceed 0.8 mm. in width and, consequently, cannot touch the ciliary body. The writers finally insist that sclerecto-iridectomy is the operation for chronic glaucoma and not for the acute disease; after so many repetitions of this limitation, they profess astonishment that some operators fail to reserve the fistulizing method of the Bordeaux School for chronic glaucoma and for it alone.

Diseases of the Optic Nerve in Cerebral Syphilis.—ELEONSKAJA (*Russk. Ophth. Jour.*, 1922, 1, 280) found in 100 cases of choked disc cerebral syphilis as the cause in 33 (12 females and 21 males); in 26 of these the nerve affection was bilateral and in 3 monolateral. In 3 cases which came to section, gumma of the brain was found; in 2 hydrocephalus internus; in 1 congenital lues. Of the remainder observed during life alone, in 8 there were indications of basilar meningitis, in 10 no definite localization and in 8 no objective signs whatever on the part of the central nervous system. As regards the remaining cerebral nerves, there was present in 9 oculo-motor paresis, in 7 abducens paresis, in 1 facial hemianesthesia, in 1 disturbances of smell and hearing, and in 1 paresis of the facial. Under specific, usually combined, treatment in the majority of cases there was improvement in the appearances of the papilla; the visual acuity improved, however, in cases only where treatment had been begun sufficiently early. Neuritis of the optic nerve was observed in cerebral syphilis only 8 times (6 males and 2 females), of which 5 were bilateral, 2 monolateral and 1 in combination with choked disc of the opposite side. Disturbances of vision were absent in 2 of the cases, in 2 there was complete blindness, in 2 vision equalled $\frac{1}{100}$ and in 2 the determination of the visual acuity was impossible on account of the severity of the general disease. In 2 the inflammation of the nerve began in the course of the first year following infection, in the remaining 6 cases in three, six and twelve years respectively after infection. All the cases presented grave involvement of the central nervous system (cephalalgia, confusion, vomiting, palsies of the extremities, cerebral nerves, etc.). Specific treatment caused improvement in the general condition in all of the cases. But the visual acuity became normal in 2 only, the remainder eventuated in more or less marked optic atrophy with corresponding diminution of the visual acuity (0.1 and worse).

The "Laughing" Sign Shortly after the Extraction of Cataract.—CHARLIN (*Annal. d'ocul.*, 1923, 16, 629) remarks that extraction of the lens, even under the best conditions, is a procedure subject to numerous accidents the results of which are always problematical for the success of the operation; it is difficult without ophthalmoscopic examination to arrive at a prognosis with any degree of certainty. Such an examination cannot be made before the expiration of a week, for the reason that it is not prudent to undertake a prolonged investigation before the formation of a firm corneal cicatrix. There is, however, a sign easily and rapidly obtained which assures a quite satisfactory prognosis at

the first change of the bandage, twenty-four to forty-eight hours after operation. It is made as follows: The patient is requested to look at the surgeon's face; the vision will be very confused; if now a strong convex lens, say +13 D, is held before the eye, the patient immediately receives a quite sharp image upon his retina; this pleasant surprise is so unexpected that he is unable to restrain a burst of laughter; this reflex laugh indicates a healthy condition of the deeper membranes. Temporary opacities of the media, such as intraocular hemorrhages and masses of cortex in the pupil, may interfere with the formation of an image and the interposition of the lens will produce no improvement in the vision; such a negative result has, however, only a limited value. Reflex outbreak of laughter is a favorable early postoperative indication of the success of the operation.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Disposition of Ureters in Renal Tuberculosis.—When a nephrectomy is performed for renal tuberculosis what should be done to the ureter? This question has been asked by many surgeons for many years and many answers have been forthcoming, usually based upon personal opinion rather than on careful follow-up studies. It will be of interest, therefore, to consider a report of WALTERS (*Minn. Med.*, 1923, 6, 307), of the Mayo Clinic, based upon replies received from 282 patients operated upon between 1915 and 1920. Ligation of the ureter with catgut and sterilization of the cut end with the cautery seems to have been the most effective means of treating the tuberculous ureters that were not sufficiently strictured to produce distention. In 48 per cent of these cases there was primary union of the incision before the patient was dismissed from observation and the incisions remained healed without subsequent drainage. Twenty-seven per cent of the patients similarly treated and whose incisions were draining when they were dismissed (from three to five weeks after operation) report subsequent permanent healing of their wounds. As might be expected, one of the least effective methods of treating the tuberculous ureter from the standpoint of wound-healing is sealing the cut end of the ureter for from forty-eight to seventy-two hours by leaving two pairs of forceps on the renal pedicle, which is too short to be ligated accurately and securely. This method was necessary in 28 cases. In 13 other cases the incision healed after the patients had been

material was grown anaërobically for four days in ascites broth and then subcultures were made on goat blood agar slants. The culture was repeatedly plated out on blood and ascites agar, and the colonies were well separated in ascites agar with and without fresh kidney tissue to insure a pure culture. It was found that the organism was an obligate anaërobe, growing at 36° C., but not at room temperature. A slightly offensive odor emanated from successful cultures. The bacillus was extremely pleomorphic, forming straight and wavy, non-motile threads of various lengths, the bacilli and filaments staining blue with Giemsa stain, and bodies within the organisms bright pink. Under certain conditions these bodies appeared to fall out of the threads and developed into motile spirilla with from 1 to 10 curves. More frequently the spirilla developed from the bodies in the interior of the cell and later emerged from the end of the thread, or the filament ruptured, liberating them. The spirilla then seemed to degenerate, and by Giemsa stain, showed inside and out elongated, slightly pointed blue bodies containing deeply staining granules at their ends, resembling short fusiform bacilli, seen in early cultures. The spirillar and bacillary cycles appeared to be connected also by a symplastic stage, when a mass of bodies was formed due to changes in the organisms, from which bacilli and threads emerged. The authoress concludes by stating that "these observations tend to confirm the theory that fusiform bacilli and spirilla are different forms in the life cycle of one organism."

Studies of Fusiform Bacilli and Spirochetes. Occurrence in Tonsils and Adenoids.—Fusiform bacilli and spirochetes in connection with actinomyces-like granules of the tonsils having been noted by DAVIS (*Jour. Infect. Dis.*, 1914, 14, 144) and later, in another series by PILOT and DAVIS (*Ibid.*, 1918, 23, 231) in 25 per cent of extirpated tonsils, PILOT and BRAMS (*Ibid.*, 1923, 33, 134) undertook to determine the frequency of these bacteria in excised tonsils and adenoids. Accordingly, the tonsils of 100 children and the adenoids from 46 of the same children were studied. Actinomyces-like granules were found in 19 per cent of the tonsils, but in only one mass of adenoid tissue, such a low incidence in the latter being attributed by the authors to the nature of the structure of the adenoids, with its folds hanging free in the nasopharyngeal vault, permitting of excellent drainage. Tonsillar smears and cultures were made from the bottoms and sides of the crypts. In the actinomyces-like granules, filaments, short fusiform bodies, typical fusiform bacilli, spirochetes and Gram-positive cocci comprised a constant, striking characteristic of these masses, illustrating a remarkable symbiotic relationship. Cultures were made by inoculating blood-agar slants. Fusiform bacilli were found in 82 per cent of the extirpated tonsils and in 32.6 per cent of the adenoids. Spirochetes appeared in 25 per cent of the tonsils, particularly in the actinomyces-like granules, and in 4.34 per cent of the adenoids. Associated with them in both tonsils and adenoids were streptococci of the hemolytic and viridans types and other bacteria. In morphology, the fusiform bacilli and spirochetes resembled those encountered about teeth and in certain putrid and gangrenous processes of the mouth and respiratory tract. The authors conclude by saying that "the tonsils and adenoids may be important sources of infections with these organisms and associated bacteria."

Studies in Fusiform Bacilli and Spirochetes. Occurrence in Otitis Media Chronica.—In a study of chronic middle-ear discharges, PILOT and PEARLMAN (*Jour. Infect. Dis.*, 1923, 33, 139) found fusiform bacilli usually together with spirochetes in 15 instances, in greatest numbers in the intensely fetid, purulent secretions. In the less offensive discharges, they were fewer, while in 3 cases in which the odor was distinctly foul, these organisms could not be demonstrated. Twelve cases, having chronic non-fetid discharges, did not reveal them and they were not encountered in cases of acute otitis media. The technic consisted of direct smear preparations, stained with 10 per cent carbol fuchsin, or gentian violet or by the Fontana method. The fusiform bacilli varied in length from 5 to 12 microns and tended to be Gram-positive. Cultures were obtained under anaërobic conditions in 2 instances. On smear, the spirochetes were not as numerous as the bacilli, being absent in 3 cases where the bacilli were present. Varying considerably in form, some exhibited 2 to 5 turns, others 5 to 15. In morphology both the bacilli and spirochetes resembled those found in Vincent's angina, pulmonary gangrene, and about normal teeth and tonsils. The authors believe that the pathway of infection is along the Eustachian tube from the naso-oro-pharynx, as these organisms could not be demonstrated in the normal canal; and that the ordinary pyogenic bacteria prepare the soil for the anaërobic, inasmuch as the bacilli and spirochetes were never found in pure form.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Housing and Health.—WALKER (*Am. Jour. Pub. Health*, 1923, 13, 897) studied the relation between our health and our environment based upon the prevalence of disease in the city of Detroit with special reference to the influence of the type and sanitation of dwellings upon disease. In the early part of the present century, the author states, we passed through a period when many ills were attributed to housing. Plumbing codes were written with great rigidity. Diphtheria and scarlet fever were attributed to leaky and defective plumbing which permitted sewer air and gas to escape into the room. Lack of ventilation and foul odors were blamed for tuberculosis and malaria. With the greater knowledge of the germ theory of disease and the modes of transmission, the pendulum swung to the other extreme when direct

contact, or at least very close contact, was held to be of prime importance in disease transmission and prevalence. The time is now at hand for the proper correlation of these factors relative to housing. The data presented indicate quite clearly for the period covered a relationship between sanitary environment and infant mortality, tuberculosis and pneumonia, which should not be considered lightly. Secondly, the relation of light to the development of rickets and the general welfare of child-life has become an established fact. The results of this study should be sufficient to stimulate interest in the improvement of housing conditions, and the formulation of housing codes, which will insure the lighting of all rooms used for habitation to an extent equal at least to 0.5 of 1 per cent of the outside light intensity.

Vaccination Technic and Certification.—GRUBBS (*Pub. Health Reports*, 1923, 38, 2201) discusses vaccination from the standpoint of the maritime quarantine officer especially and describes the procedure in use at the New York Quarantine Station. The reactions of immunity are described briefly and the point is brought out that as soon as one of these reactions enables one to judge of the immunity of the individual the person may be released; in other words, vaccination is used not only "to produce immunity but also to measure it." The following are the conclusions: (1) By making use of the reactions that follow vaccination, it is possible to eliminate much of the delay now considered necessary to prevent the spread of smallpox; (2) in order to encourage vaccination, these reactions should be observed and records should be furnished the individual as a proof of his immunity; (3) a person certified as immune to smallpox should not be detained by any smallpox quarantine.

Results of a Three-year Trachoma Campaign Begun in Knott County, Kentucky, in 1913.—McMULLEN (*Pub. Health Reports*, 1923, 38, 2463) states that in 1912, among 4000 persons examined, 500 or 12½ per cent had trachoma. As a result of surgical treatment the disease has been practically eradicated. A survey recently shows that the treatment had been permanently successful in the great majority of cases, and that in about ten years the disease had been practically eliminated in a badly infected region.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL*.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript*.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

APRIL, 1924

ORIGINAL ARTICLES.

ALCOHOL A FACTOR IN ELIMINATING RACIAL DEGENERACY.

BY CHARLES R. STOCKARD, PH.D., M.D.,
CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

HAS the use of alcohol during past generations actually injured the physical or mental quality of the present generations? Or, has its use actually benefited or improved the quality of the present generations in this country? These are fundamental questions and are not to be answered in the realms of religion, politics, sentimentalism or prejudice. They are scientific questions and are to be answered only by careful investigation.

The study of human alcoholism is complicated in many ways and particularly by the fact that severe alcoholism generally appears in individuals with unstable or degenerate nervous systems. In other words, it is almost impossible to be certain that the alcohol has acted upon an individual possessing the average normal constitution. When one critically scrutinizes the records and works back on the family histories of abnormal children and the degenerate descendants of chronic alcoholics, the element of already present familial degeneracy is almost invariably there. The production of abnormal or degenerate human beings as a direct result of alcoholism has never been demonstrated in a satisfactory manner from the scientific standpoint. Until individuals of the most vigorous physical stocks have acquired severe alcoholism and later mated with similar vigorous persons to give rise to abnormal offspring, we cannot be certain that human alcoholism has produced degeneracy. The result of such matings is not available among human records and

in order to analyze the problem recourse must be had to the lower mammals.

During the past thirteen years a continuous experiment has been conducted in an effort to determine whether severe alcohol treatments would modify the course of normal development and whether such treatments would affect the germ-cells of the species.¹ Guinea-pigs have been used as the animal material in this study and more than 100 individuals have been systematically treated with alcohol for periods of from a few months to as long as six years. Records are now available from more than 5000 animals in the various generations of the experiment. But, as might be expected in the analysis of so complex a problem, the results have not always been easily interpreted and only after the study of a number of generations is the actual effect of the alcohol treatment on the racial stock definitely determined.

In considering the effects of alcohol on a guinea-pig, it should be borne in mind that the sex-glands and germ-cells of such a mammal are placed in the body in similar positions and are protected against their surroundings in the same way as in man. The type of placenta and its attachment to the uterine wall are closely similar in man and the guinea-pig. It is highly probable that toxins contained in the blood or fluids of the guinea-pig body would reach the germ-cells or the developing embryo by the same routes as in the human, if they reached them at all.

The dosage or degree of treatment necessary to produce similar results would no doubt differ widely between the guinea-pig and man. However, this is only a difference in quantity and very probably when the effective dose is reached for the two animals the results would be similar. At any rate, all the visible physiological effects of acute alcoholic intoxication in man are similarly exhibited by the guinea-pig. Wide variations in individual tolerance and other well-known human reactions to alcohol are shown by these animals.

Methods of Control. In experiments such as we are to consider, the quality of the animals employed and their hereditary histories and relationships are of fundamental importance. Pedigreed guinea-pigs have been used which were obtained from eight different sources. Before the treatments are begun the animals are mated normally in order to test their fertility and the quality of offspring. They are then separated into control and experimental groups. The controls are of the same blood lines as the alcoholic stock. Brothers and sisters, parents and offspring are in the two groups, and actually in some cases the same individuals have first been used in the control and later in the experimental groups. There can be

¹ Stockard, C. R.: Arch. Int. Med., 1912, 10, 369; Am. Nat., 1913, 47, 641; Stockard and Papanicolaou: Am. Nat., 1916, 50, 65; Jour. Exp. Zool., 1918, 26, 119; Brit. Med. Jour., 1922, II, 255.

no doubt that any original defect or weakness that may have been in the stock from which the alcoholic animals were derived must also have been in the control stock, since the stocks are in all cases actually the same. The tabulated records are from animals with no inbreeding in either the control or alcoholic lines.

Treatment. The guinea-pigs are treated with the fumes of commercial 95 per cent alcohol to the point of intoxication six days per week for various lengths of time. Several have been treated for as long as six years and certain of the treated animals have lived to become more than seven years old, which is the longest life span recorded for a guinea-pig as far as I know. The fumes are inhaled while the animals are confined in a treatment tank and all ill-effects on digestion which would accompany the administration of alcohol by stomach are thus eliminated. Many of the animals have been treated with alcohol by stomach but their digestion is disturbed and conditions arise which complicate the experiment.

The daily inhalation of alcohol fumes does not injure the health or activities or to any degree shorten the life of the treated guinea-pigs. The records of offspring and later descendants of such treated guinea-pigs are, however, distinctly different from the control records. Thus the alcohol affects the germ-cells in some way in spite of the fact that no deleterious effect on the body or life of the treated animal is discernible.

The records which indicate that the germ-cells of these treated animals have been affected or modified by the alcohol treatment will first be presented. We may then consider the nature of this modification and the bearing the results have on the problem of racial quality. Certainly there is no question of greater importance than the physical quality of the units composing the race.

The Progeny of Animals Paired Alternately with Normal and Alcoholic Mates. The simplest and clearest way of ascertaining whether the treatments do actually affect the male germ-cells is by a comparison of the offspring arising from a normal mother mated alternately with normal and alcoholic males. The action on the female germ-cells or ova may also be tested by allowing normal males to sire offspring by alternate service to normal and alcoholic females. Table I gives such records from normal animals that have been alternately paired with alcoholic and normal mates.

When the same normal male guinea-pigs were mated 81 times with normal females and 81 times with alcoholic mates the records were widely divergent. The 196 young born from the normal combination showed a mortality during the first three months of less than 23 per cent and none of these offspring were defective. (Guinea-pigs are mature at about three months old, and animals that attain this age usually survive as adults.) Of 185 young sired by the same normal fathers mated with alcoholic mothers, 56.6 per cent, or only a few more than half, lived to reach maturity. The mortality

here was about double that from normal mothers, being 43.3 per cent as against 22.9 per cent. Almost 6 per cent of these offspring were structurally defective while none from the normal combination showed any such defects.

TABLE I.—ALTERNATE MATINGS OF NORMAL ANIMALS WITH NORMAL AND ALCOHOL MATES.

	Matings of 35 normal males alternately with		Matings of 44 normal females alternately with	
	Normal females.	Treated females.	Normal males.	Treated males.
Number of matings	81	81	77	81
Total offspring	196	185	195	182
	2.42 av. lit.	2.28 av. lit.	2.53 av. lit.	2.25 av. lit.
Failure to conceive	6	6	3	10
	7.90%	7.90%	3.89%	12.34%
Lived over three months . .	151	105	161	118
	77.03%	56.64%	82.56%	64.83%
Died under three months . .	45	80	34	64
	22.96%	43.35%	17.45%	35.16%
Defective	0	11	0	9
		5.95%		4.97%

Still more striking data are obtained when the male germ-cell or spermatozoon is subjected to the effects of the treatment. In such cases we have the records from 44 normal females mated alternately with normal males and alcoholic males. The same normal mothers produced all the offspring. There were 77 normal matings which produced 195 young and there were only 3 failures to conceive. Eighty-one matings of the same females with alcoholic males gave only 182 young, and over 12 per cent of these matings failed to result in conception. There was a mortality of 17.4 per cent among the offspring of the normal matings, while the alcoholic fathers sired offspring that suffered a mortality twice as high, being 35.1 per cent. Nine of the offspring from alcoholic fathers were defective, but none from the normal sires.

This difference between the records of offspring from the same normal individuals when paired with normal and alcoholic mates clearly demonstrates an injurious action of the experimental treatments on some of the germ-cells of these mammals. We may further analyze very briefly the action of these effects during later generations.

Effects on Later Generations, the Improvement of the Stock. We shall consider the records of animals occurring in the different generations of the alcoholic stock during the tenth, eleventh and twelfth years of the experiment. The experiment taken as a whole has always given substantially the same results. Anyone familiar with the breeding records of these mammals will recognize the high quality of the normal control stock used in this study. The young are produced in litters of from 1 to 5, the average size litter

being about 3, exactly 2.72. The animals are large and well developed at birth, the average litter weight being 188.85 gm., so that the average individuals weighs at birth about 65 gm. During the period considered 506 control animals are recorded. The total mortality under three months of age was only 22 per cent. It is important to note that about one-half of the mortality occurred before birth and about one-half between birth and maturity. This 50-50 ratio between prenatal and early postnatal mortality is typical for the normal control guinea-pigs. The prenatal mortality consists of abortions, uterine absorptions, which may be very accurately detected by careful palpation, and still-born young.

Among 1197 progeny from alcoholic ancestry the average litter size is somewhat smaller than the control; there has been more early elimination of the weaker embryos. The size of the young at birth is not very different from the control. The total mortality under maturity is almost twice as great for these descendants of alcoholics as for the control animals, being, after correction for litter size, 180 against the control 100. The actual mortality is 38 per cent against an expected mortality of 21 per cent.

Now, the point of great significance is that instead of the total mortality among the alcoholic progeny being divided into a 50-50 prenatal-postnatal ratio, as in the control, the prenatal deaths are double the postnatal, or are 2 to 1 instead of 1 to 1. The alcohol treatments have acted to eliminate more young than would have died normally and this elimination has been largely during the early stages of development. There are some weak germ-cells and embryos which die among the normal control stock, but some rather poor specimens in all normal stocks do not die during early life. More of the weaker embryos are eliminated from the alcoholic stock and a higher proportion of resistant or strong individuals survive among the fewer offspring produced. The alcohol is acting as a selective agent to eliminate the less hardy embryos from the stock and the result of this selective action is very clearly brought out by a comparison of the consecutive generations produced.

The offspring, F_1 , from directly treated parents show the highest mortality of all, being 195 against the normal 100, or about 43 per cent against the control 22 per cent. Here the prenatal mortality is $2\frac{1}{3}$ times the early postnatal. *Parental alcoholism has doubled the elimination of the weaker members of the progeny and more than $\frac{2}{3}$ of these have succumbed before being born.* This remarkably high intrauterine death leaves a group of animals that, in spite of the parental alcoholism, do not show a very greatly exaggerated early postnatal mortality, although it is, of course, well above the control. The control records give a prenatal mortality of only 12 per cent against the first generation alcoholics' prenatal mortality of 30 per cent, this being $2\frac{1}{2}$ times greater. While the control early postnatal mortality was 10 per cent, the offspring of treated parents

showed only a little above 13 per cent or $\frac{1}{3}$ greater than the control. *Thus treating the parents with alcohol increases the prenatal mortality of offspring almost 8 times more than it increases the postnatal mortality.* The prenatal mortality increases 250 per cent over the control while the postnatal mortality increases only 30 per cent over the control, and thereby almost all of the weaklings are eliminated before birth.

The effects of this decided attack of the alcohol on the less resistant germ-cells is strikingly brought out during the subsequent generations. The records from 747 animals two generations removed from the alcohol treatments show that the effects were actually on the germ-cells as such. The parents of these animals had not been directly treated yet the type of record is still exactly the same as from treated parents. The mortality is more than $1\frac{1}{2}$ times higher than the control, being 164 against the normal 100. The prenatal mortality is almost double the postnatal instead of being equal to it. Thus, there is an excessive elimination of the weaker individuals among the grandchildren of alcoholic animals and the elimination is chiefly exaggerated before birth.

Among animals with treated great-grandparents, the mortality is 40 per cent higher than among the control. Much over half of the total mortality, about 57 per cent against 43 per cent, still occurs before birth. Thus, in the third filial generation away from the treatment, the affected germ-cells are still being eliminated by early death of the embryos and young individuals, but 69 per cent of all the young conceived are hardy enough to survive, and not only do these animals survive but they produce offspring that actually average better than the control stock.

The fourth generation animals, descended from alcoholic great-great-grandparents, have a mortality of only 13.5 per cent against the control 21 per cent, or only 64 against the normal 100. Here, although the numbers are small, the prenatal mortality is reduced to only a little over one-half the postnatal. This is a completely reversed reaction from that shown among the early alcoholic generations and is actually better than the normal 1 to 1 ratio. *All of the weak and altered germ-cells have now been eliminated from the lines and a group of superior animals are obtained, which average well above the control.* This may not be due to an actual improvement of the best in the stock, but, at any rate, the more resistant or strong individuals have not been injured by the ancestral alcoholism and the weaker germ-cells of the population were injured and gradually eliminated from the stock. The F_4 animals are superior to the control since their numbers are not contaminated by the presence of weak individuals with low vitality such as sometimes survive in the normal or control lines of any animal stock. The alcohol acted to eliminate weakness in the stock but did not lower the quality of the good!

Alcohol acts as a selective agent to bring out a group of unusually

strong specimens and although they are possibly not quite so productive as the control, they show a record superior in vitality.

Should one desire to apply these experimental results to the human alcohol problem, it might be claimed that some such elimination of unfit individuals had benefited the races of Europe, since all of the dominant races have a definitely alcoholic history, and the excessive use of alcohol was decidedly more general three or four generations ago than it is today. That is, certain families that were alcoholic three generations ago have not been excessively so in the more recent generations.

Contrasting Records from Male and Female Alcoholics. Further significant evidence regarding the selective action of alcohol and the elimination of defective individuals is shown by contrasting the records of the progeny from alcoholized male ancestors with those from alcoholized female ancestors. When only the father was treated the average litter was small, the total mortality was 71 per cent higher than normal and the prenatal deaths were almost $2\frac{1}{3}$ times greater than the early postnatal mortality. The entire reaction is typical of the alcoholic line. Where only the mothers were treated the records are considerably worse than the records from the treated fathers. The average size of the litters was somewhat larger than from the treated males, but the actual litter weight of these larger litters was less. The individuals from alcohol mothers are small at birth. The mortality among these offspring was almost $2\frac{1}{2}$ times higher than among the control. For comparison, if the control mortality be indicated by 100, then the mortality of the offspring from treated fathers is 171, and from treated mothers 243.

If we now compare the grandchildren from treated grandfathers with those from treated grandmothers, a striking reversal is shown. Animals having only female ancestors that had been subjected to alcohol treatment show a lower mortality than those from treated male ancestors, and the prenatal and postnatal mortalities are almost equal. At first sight it would seem as though the treatments had acted more severely on the male germ-cells than on the female. But it is highly probable that the superior record of the descendants from treated females is due to the more rigorous elimination of defectives that occurred among the immediate offspring of alcoholic mothers. Among the offspring of directly treated parents the mortality was lower from treated fathers—171 against 100 as normal; and higher from treated mothers—243 against the normal 100. The descendants from the treated males which had suffered the lower mortality in the first generation subsequently show a higher mortality in later generations—188 against 132 for descendants of treated females. This simply means that when the action of the treatment is severe on the first generation, as was the case when the mothers were treated, only the comparatively hardy individuals

survive. The descendants of these hardy survivors later show a superior record in comparison with the descendants from treated males, among which the eliminations in the first generation had not been so severe.

When we consider the welfare of the race or stock rather than that of the individual, it is found that the descendants of those groups of animals which suffered the highest mortalities and thus withstood the most rigorous elimination are superior in quality to the descendants from the groups less severely affected. This individual selection furnishes a great advantage to the later generations, as is shown by the superior quality of the F_4 group of guinea-pigs.

Probable Conclusions. Just how is one to estimate the actual significance of the foregoing experimental results? Although the racial stock is really benefited or improved by the treatment of ancestors with alcohol, it might be said that such an improvement has cost very dearly so far as the great number of injured and eliminated individuals are concerned. This is true, but there is a real question as to whether it is proper or fair to save such individuals! The original quality of those germ-cells that were injured was certainly below that of those that escaped injury or may have been benefited. Now, does not the actual existence of the race in the end really depend upon ridding itself of the weight of just these individuals? Certainly the close approach to perfection of wild stock has been aided by the elimination of weak and defective specimens through the competition in nature and the survival of the fittest. It is also certain that domestic races are kept up by the careful selection of the best specimens for breeding in the stock. No stock raiser hesitates to eliminate the weak individuals, and a fast race horse is derived from a fast dam and is certainly not sired by a draft horse.

The wild races of man evolved in a selective environment and the cripples and defectives were not generally carried by the tribe. Civilization has tended to remove the agencies of severe selection and has sought to protect the individuals from original sources of natural elimination. So admirable an accomplishment as the lowering of infant mortality is partially such a performance. Are we always to continue these practices? I doubt very much that they will be continued when the necessary available food becomes a world question rather than one of a few localities. Certainly the burden on the community of providing for individuals who are actually harmful to it from a biological standpoint will become more and more intolerable as a position of practical reason is reached.

The great problem in preventive medicine may some day be the prevention of physical and mental, or structural, defectiveness. And the actual prevention of such conditions is the elimination of the germ-plasm from which they arise and the preservation of the biologically good stock.

The experimental work on the effects of alcohol on the stock shows it to be a decidedly selective agent acting to injure and eliminate only the weaker and less resistant germ-cells and [thereby it improves the quality of the race. It might be answered that if alcohol does injure the less resistant cells it would in large enough doses also injure the best cells. This is no doubt probable but here another important factor must be borne in mind and that is the question whether the mammalian blood stream can tolerate the presence of enough alcohol to injure all the germ-cell population, the strong as well as the weak. This is certainly not done by intensive treatments on guinea-pigs, which is the most definite evidence at hand. The treatments administered to these guinea-pigs in order to obtain the above results have been more severe than probably any human being has ever undergone. The treatments were usually started during adolescence and the individuals experienced daily intoxication 6 times per week through maturity, adult life and middle age. Certainly human beings rarely lead so alcoholic an existence. With full appreciation of all the difficulties in transferring, the results obtained from the study of one animal kind to another, the following seems to be a perfectly conservative and warranted deduction: It is highly improbable that human beings have ever injured or eliminated their normal resistant germ-cells with alcohol. Alcohol probably has eliminated some of the bad. Those nations of men that have used the strongest alcoholic beverages through many generations have now, from a standpoint of performance and modern accomplishments, outstripped the other nations with less alcoholism in their history. This may be due to some such selective effects as those recorded in the foregoing pages.

THE EFFECT ON THE KIDNEY OF TREATMENT FOR SYPHILIS.*

By ALBERT R. MCFARLAND, M.D.,

SECTION ON DERMATOLOGY AND SYPHILOLOGY, THE MAYO CLINIC,
ROCHESTER, MINN.

THE extent of reaction of the kidney to treatment for syphilis can only be adequately comprehended by reviewing the usual classifications of renal lesions. Needless to say, this subject has been the topic of much argument since the first classification of diseases of the kidney by Bright in 1827. Even though much

* Thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology, May, 1923.

confusion still exists, a summary of existing opinion is not without value.

One of the older classifications which seems worthy of consideration is that of Delafield. His observations are based on wide experience, pathologically and clinically, and were first presented in 1882 in his book *Studies in Pathological Anatomy*. A later publication on the same subject appeared in 1903 under the title of *Lectures on the Practice of Medicine, with Cases and Charts*. These later views coincide almost entirely with his earlier observations. His classification is as follows:

1. *Acute Congestion of the Kidney*. This type of reaction is found after the administration of turpentine or cantharides, following removal of one kidney, in which a compensatory congestion of the remaining kidney occurs, and following major surgical operations. It is characterized by engorgement of the bloodvessels, with the appearance of albumen, casts and erythrocytes in the urine, and diminished urinary output. Recovery is the rule.

2. *Acute Degeneration of the Kidney*. This type of reaction takes place after the administration of such poisons as mercury, arsenic or phosphorus. It is characterized by diminished urinary output and the appearance of albumen, casts and erythrocytes. The specific gravity remains unchanged. The function of the kidney is not impaired, and if the dose of the drug is sublethal the kidney returns to normal. In other words, the patient usually recovers completely, or dies. The pathological condition consists of degeneration or death of the epithelial cells of the renal tubules. Edema of the skin or anasarca occurs if the renal process is sufficiently extensive.

3. *Acute Exudative Nephritis*. This form of pathological change occurs with the toxemia of pregnancy, and in diseases such as scarlet fever and diphtheria. There is acute congestion of the kidney with exudation of serum and cells. Pathological changes are found both in the tubules and in the glomeruli. Large numbers of casts, albumen and pus are found in the urine. There are increased blood-pressure and edema, and cerebral and gastrointestinal symptoms.

4. *Acute Productive Nephritis*. This type of nephritis is characterized, for some unknown reason, by a tendency from the beginning to a production of fibroblasts and new connective tissue, which ultimately results in permanent embarrassment of renal function.

5. *Chronic Congestion of the Kidney*. This type differs from acute congestion only in degree of engorgement and in duration. It is of importance mainly in that it may lead to chronic nephritis.

6. *Chronic Degeneration of the Kidney*. Wasting disease, such as tuberculosis or malignancy, is largely responsible for this type. The pathological condition is chronic degeneration of the tubules. The glomeruli are not involved. A slight amount of albumen is

found in the urine; the blood-pressure is normal. There is no edema.

7. *Chronic Nephritis*. The cause of this type of disease is indefinite, but probably results from a number of toxic and metabolic factors often incident to advancing age, exposure and various repeated renal insults. It is characterized by chronic degeneration of the tubular epithelium, contracture of the glomeruli, increase in interstitial connective tissue and damage to the bloodvessels. Chronic nephritis, from a clinical point of view, cannot be classified according to Delafield, in respect to the degree of involvement of any of these structures. There are, however, two subdivisions which can be made clinically: chronic nephritis, in which exudation occurs, and chronic nephritis, in which it does not occur. The former is characterized by a large amount of albumen, extreme edema, with exudation into the serous cavities, cardiac hypertrophy and in some cases elevation of blood-pressure; with the latter there is but little albumen in the urine, very little edema or anasarca, and high blood-pressure, cardiac hypertrophy, emphysema and arteritis result.

The classification of Senator, as given by Musser and Kelly, is simple and well known to most physicians. It is as follows:

I. Acute nephritis.

II. Chronic nephritis.

1. Chronic parenchymatous nephritis, or chronic diffuse nephritis without induration.

2. Chronic interstitial nephritis or chronic diffuse nephritis with induration.

(a) Primary chronic interstitial nephritis.

(b) Secondary chronic interstitial nephritis.

(c) Arteriosclerotic kidney.

3. Diffuse nephritis, a combination of Forms 1 and 2.

Volhard and Fahr's classification of renal diseases, which is widely used by clinicians, differs somewhat from that of Delafield, and is as follows:

1. *Nephrosis*. This group includes all purely degenerative processes of the kidney. It is caused by various poisons, either mineral, bacterial or metabolic, or it may occur without detectable cause. In the first stages there is cloudy swelling of the tubules, a small amount of albumen and a few casts. In a later stage epithelial degeneration takes place. Fatty degeneration of the tubules and disappearance of the cell nuclei may be seen. Later, definite evidence of inflammation may appear, which consists in an increase of vascular connective tissue and degeneration of the tubular epithelium; the glomeruli are normal. Only in the last stage of the disease is there evidence of interstitial overgrowth and glomerular damage, and that is due to secondary contraction. Nephrosis is characterized by albumen, casts and erythrocytes in the urine,

present to a degree proportionate to the amount of involvement. The tubular epithelium is the chief point of attack. Edema is characteristic of the advanced stages. The blood-pressure is not elevated and renal functional tests are normal. Anorexia and watery diarrhea appear in well-marked cases. Eye-ground changes do not occur, and recovery is the rule. Several subdivisions of the main group of nephrosis may be added, such as secondary nephrosis, in which the offending agent is well known; characteristic nephrosis, with which unique pathological pictures occur, such as glycogen deposits in diabetes, necrotizing nephrosis seen in bichloride poisoning, and complicated nephrosis, of which the amyloid kidney is an example.

2. *Nephritis*. This type of the disease is characterized chiefly by glomerulonephritis, of which there are three stages: (a) Acute nephritis in which the glomeruli are principally involved; slight degeneration of the epithelium and slight increase in connective tissue may also occur. (b) The condition may later pass into the second or chronic stage, with increase in the interstitial tissue and advanced changes in the glomeruli and tubules. (c) The last, or end-stage, with advanced changes in glomeruli, tubules and interstitial tissue. In this stage hypertension appears; edema is not uncommon; there are blood, albumen and casts in the urine, and the renal function is impaired with increase of rest nitrogen; the eye-ground changes are characteristic.

To the group of glomerulonephritis may be added a second group of focal glomerulonephritis, in which a small area of the kidney is involved, a slight albuminuria usually being the only finding. Septic interstitial focal nephritis may appear as part of general sepsis, and embolic focal nephritis may occur in endocarditis. A third group includes sclerosis of the kidney, consisting of primary sclerosis of the vessels. In the simple type there is cardiac hypertrophy and increase in blood-pressure, but the rest nitrogen is normal, renal function is good and eye-grounds are normal. The principal danger, from a clinical point of view, is that of vascular accidents. If the primary sclerosis is complicated by secondary nephritis there is added to the picture loss of flesh, anemia, cerebral symptoms, rise in rest nitrogen, impaired renal function and ultimately uremia.

Floyd has emphasized the differences in conception of these two classifications in a careful analytical study. Volhard and Fahr conceive of the pathological changes in the kidney as falling into three main groups: (1) Nephrosis, in which the tubular epithelium is chiefly attacked; (2) nephritis, in which the changes are primarily glomerular; (3) sclerosis, in which the blood supply is the chief point of attack. Delafield, on the other hand, conceives of the kidney as being either acutely or chronically inflamed, and makes the classification depend on whether the kidney is of the exudative,

degenerative or proliferative type. He also adds to his classification, acute and chronic congestion.

Kolischer, in his classification, adds to the foregoing groups—pyelitis and pyelonephritis—which, of course, must be kept in mind as an integral part of renal lesions.

Epstein's classification is in most points similar to that of Volhard and Fahr, but he calls attention to a type of chronic nephrosis in which myxedema plays a part, and which must therefore be considered from the endocrine point of view.

Fischer places less emphasis on the particular type of renal tissue involved in renal diseases, but conceives of all types of nephritis as parenchymatous. Thus, in focal nephritis only a part of the parenchyma is involved. In vascular disease the parenchyma is affected secondarily through the vascular changes. In toxic conditions the parenchyma is reached by way of the blood and lymph streams.

Effect of Mercury and Arsphenamine on Renal Activity. The study of the effect of treatment for syphilis on the kidney resolves itself largely into the effect of mercury and arsphenamine on renal activity. According to the foregoing classifications, the action of these drugs has been found to cause the pathological condition known as nephrosis or degeneration of the kidney. According to past experience in dealing with the normal kidney, therefore, the effect of arsenic and mercury has been found to consist of degeneration of the tubular epithelium, with the presence of casts, albumen and pus in the urine, edema in the later stages, normal renal function, normal rest nitrogen and either complete recovery or death.

However, in the series of cases reported here the problem is complicated by the type of case with which one has to deal. Syphilitic patients are encountered who have focal nephritis, chronic nephritis, primary sclerosis, acute nephritis of intercurrent infection, nephrosis and pyelitis or pyelonephritis, as well as normal kidneys. The problem as it presents itself is, therefore, that of ascertaining the action of antisypilitic drugs on normal and abnormal patients, the relative damage done to each and the relative permanency of this damage. A group of patients who have renal complications of definitely syphilitic origin is also encountered. This group is of sufficient importance to deserve special discussion at this point. The most important type of syphilitic lesion of the kidney is acute syphilitic nephritis. Waldorp and Behr add to the acute syphilitic changes of the kidney, the multiple fibrous type or gummatous type of kidney, primary syphilitic sclerosis of the renal vessels, interstitial syphilitic nephritis and paroxysmal hemoglobinuria. Acute syphilitic nephritis seems to have been demonstrated as a clinical entity beyond all reasonable doubt. The later changes, such as gumma and syphilitic sclerosis, unless confirmed

at necropsy, must be regarded with more or less doubt in a given case, since therapeutic response is here complicated by many factors, such as rest, diet and the tonic effect of arsphenamine, which are a part of the treatment for syphilis employed in the Mayo Clinic.

Stengel and Austin, in 1915, made some interesting observations on the probable syphilitic nature of certain cases of chronic nephritis in syphilitics. Their study largely hinged on the observation of doubly refractile lipid bodies in the urine, to which attention had been called by Munk. In 6 cases, in which there was definite evidence of nephritis and also syphilis, they found doubly refractile lipid bodies in every instance. In 14 non-syphilitic cases, in which there was nephritis, there were lipid bodies in 5. Stengel and Austin assert, however, that only 1 case was encountered in which syphilis was absent, and yet large amounts of doubly refractile lipid bodies were found. Aside from this series of cases, in which a special study was made of the lipid bodies, most of the instances in the literature of chronic nephritis of syphilitic origin are open to more or less suspicion. Weisfelt, for example, has reported the case of a man, aged forty-eight years, with fever, dyspnea, insomnia, ascites and anasarca. The urine contained 1 per cent albumen, and the Wassermann reaction was positive. There was no response to treatment for syphilis and the case terminated fatally. One wonders whether evidence is sufficient in such a case to warrant the diagnosis.

The response of the kidney in cases of acute syphilitic nephritis to treatment for syphilis is the chief and final diagnostic phenomenon in this condition. Mercury seems to be the less desirable because of its slow action and high renal toxicity. Arsphenamine, on the other hand, has the advantage of having a rapid action on the spirochetes and less toxicity for the kidney. A case previously reported by Stokes illustrates the advantage of arsphenamine over mercury. Mercury, according to his experience, may prove beneficial for a time, but recurrence is prone to occur, and permanent results are difficult to obtain. The margin of safety between the therapeutically efficient and the toxic dose is also very narrow. In using arsphenamine the dosage should be small and given at comparatively frequent intervals. If given in too massive doses renal embarrassment may result. Neoarsphenamine is probably preferable. No case was encountered in this series which could be considered true syphilitic nephritis. I wish to call attention, however, to two cases which had many points in common with this condition, and which also illustrate the care which must be exercised in diagnosis.

CASE A280104 (reported by Stokes).—It will be noted that this case might well have passed for genuine acute syphilitic nephritis,

except for the fact that no permanent therapeutic response to treatment was obtained.

CASE A251644.—The condition also did not respond to treatment for syphilis, although nephritis developed during the latter part of treatment.

As has been indicated, therapeutic response is the crucial point in the diagnosis of acute syphilitic nephritis—a fact which has served to establish this condition as an entity. Karvonen, Fournier and Hoffman were among the first to recognize it. By this standard Karvonen could only accept as authentic 25 cases out of 92 which had been reported as such. Fournier reported 26 cases from his experience, and Hoffman had seen only 6 cases up to 1913. Since then cases have been reported by Stokes, Symmers, Cole, Day, Elliott and Todd and Silverman. Aside from the therapeutic response, other points to be emphasized in the diagnosis of acute syphilitic nephritis are the presence of early syphilis, acute nephritis, the elimination of any other possible cause and special phenomena, such as doubly refractile lipid bodies in the urine and perhaps spirochetes in the sediment of catheterized specimens of urine.

Reaction of Apparently Normal Kidney to Arsphenamine and Mercury. A series of 128 patients receiving 271 individual courses of treatment was studied to determine the effect of arsphenamine and mercury on the normal kidney. So far as could be determined, there was no evidence of renal damage or irritation in any of these cases. The urine was normal on a single examination of a twenty-four-hour specimen; blood-pressure was within normal limits. There was no evidence of marked arteriosclerosis, and no clinical evidence of nephritis. The treatments to which the patients were subjected consisted of arsphenamine or neoarsphenamine and mercury, administered at the same time. The usual arsphenamine course consisted of six injections given at weekly intervals, ranging in dosage from 0.4 to 0.6 gm. The mercury was given either in the form of intramuscular injections of mercury succinimide, $\frac{1}{6}$ to $\frac{1}{4}$ grains daily, or as 30-grain mercurial inunctions, six a week in courses of forty to eighty. The evidences of renal irritation or damage discussed do not include an exhaustive study of renal function, but are at least those criteria which are most commonly employed and available in therapeutic practice. The factors studied were the presence of casts, albumen, pus cells and erythrocytes in the urine, evidence of increased blood urea or urea nitrogen, phenolsulphonephthalein excreting power, evidence of edema and the presence of nausea, headache, depression or other subjective symptoms of severe renal impairment.

Throughout this study the grade of urinary abnormality in individual items is recorded on a scale of 1 to 4.

From the standpoint of frequency of pathological constituents in aggregate treatment, in the 271 courses given to 128 patients with normal kidneys the following results were obtained. There were no hyaline or granular casts present in 57 of the courses; casts 1 were present in 88; casts 2 in 71; casts 3 in 36; casts 4 in 19. In other words, on the basis of the 271 courses there were casts 2 or above in 46 per cent. In 84 courses there was no albumen present; in 143 courses there was albumen 1; in 37, albumen 2; in 7, albumen 3; in no course was there albumen as high as 4. There was, therefore, albumen 2 or above in 16 per cent.

In 71 courses no pus was found; in 157 there was pus 1; in 35, pus 2; in 6, pus 3, and in 2, pus 4. There was, therefore, pus 2 or above in 15 per cent. Only four times in the 271 courses were erythrocytes present.

In 271 courses given to 128 patients who had normal kidneys, but who reacted definitely to treatment, 46 per cent had a very marked increase in hyaline and granular casts under intensive combined arsphenamine and mercury treatment; 16 per cent had a marked rise in albumen, and 15 per cent a marked increase in pus cells. Erythrocytes were rarely present and few in number.

From the standpoint of the individual patients, in only 35 of the 128 cases were the urinary findings sufficiently abnormal to call for the determination of the blood urea, and phenolsulphonaphthalein excreting power. With only two exceptions, the phenolsulphonaphthalein was above 40 per cent, and the blood urea was below 30 mg. for each 100 cc. In 1 case the phenolsulphonaphthalein output was 35 per cent in two hours and fifteen minutes, and the blood urea 34 mg. per each 100 cc of blood. In the other case the intramuscular phenolsulphonaphthalein was 35 per cent, and the blood urea 60 per cent.

In no case was there evidence of severe renal damage, as indicated by edema, toxic headache, nausea, vomiting or impending coma. The blood-pressure estimations were not recorded in a sufficient number of cases to afford reliable data, but in a few cases in which comparative readings were made there was no change in the readings.

Fig. 1 illustrates a typical case of renal irritation while under combined arsphenamine and mercury treatment.

As has been noted, these patients were treated with mercury and arsphenamine or neoarsphenamine; the majority received arsphenamine, only 6 per cent receiving neoarsphenamine. This number is, perhaps, too small from which to draw definite conclusions, but it was found that only 23 per cent of the patients developed casts 2 or above; 23 per cent, albumen 2 or above; 18 per cent, pus 2 or above. In a larger series these data might be different,

but in general it would seem to indicate that neoarsphenamine is less toxic to the kidney than arsphenamine. This fact has been noted by other investigators (Kolmer and Lucke).

The question suggests itself as to whether there is an increasing tendency for the kidney to react to arsphenamine and mercury as the combined treatment of the patient progresses. This point was studied with regard to 54 patients who fulfilled the following requirements:

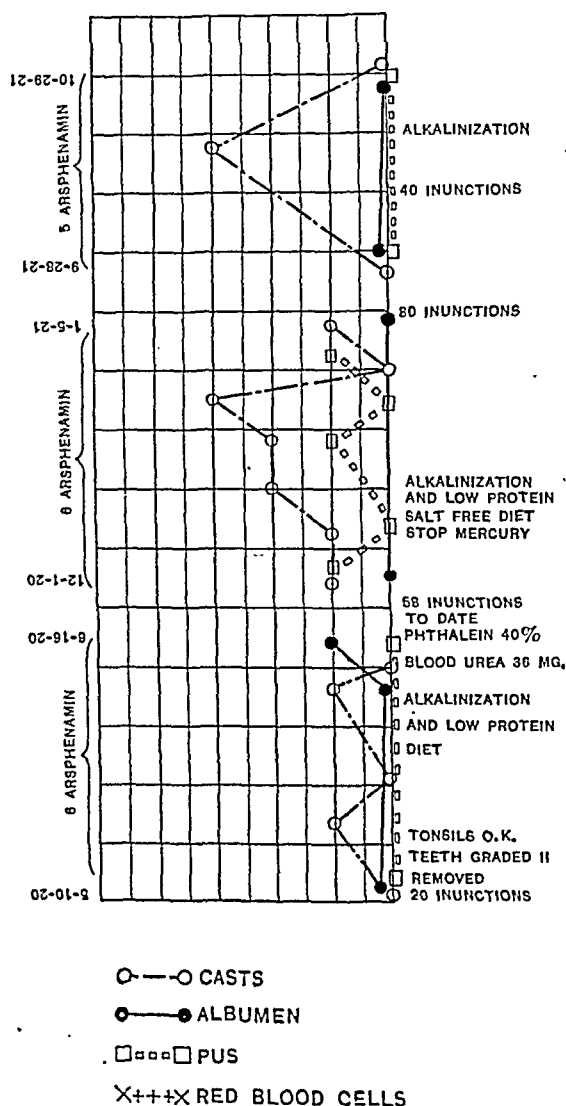


FIG. 1.—Case A313244. Characteristic irritation reaction of normal kidney under treatment for syphilis. Note the pressure of casts without other abnormal findings.

They had normal kidneys at the outset, they had all received two courses or more of treatment for syphilis and they had received both mercury and arsphenamine during each course. In 30 of the 54 cases there was a tendency for casts to increase, in 22 for albumen to increase and in 7 for pus to increase. In 14 cases

there was a tendency for the casts to decrease, in 7 for albumen to decrease and in 9 for pus to decrease. In 11 cases the casts remained the same, in 26 the albumen remained the same and in 39 the pus remained the same. Thus there was a tendency for the casts to increase as the courses progressed in 55 per cent of

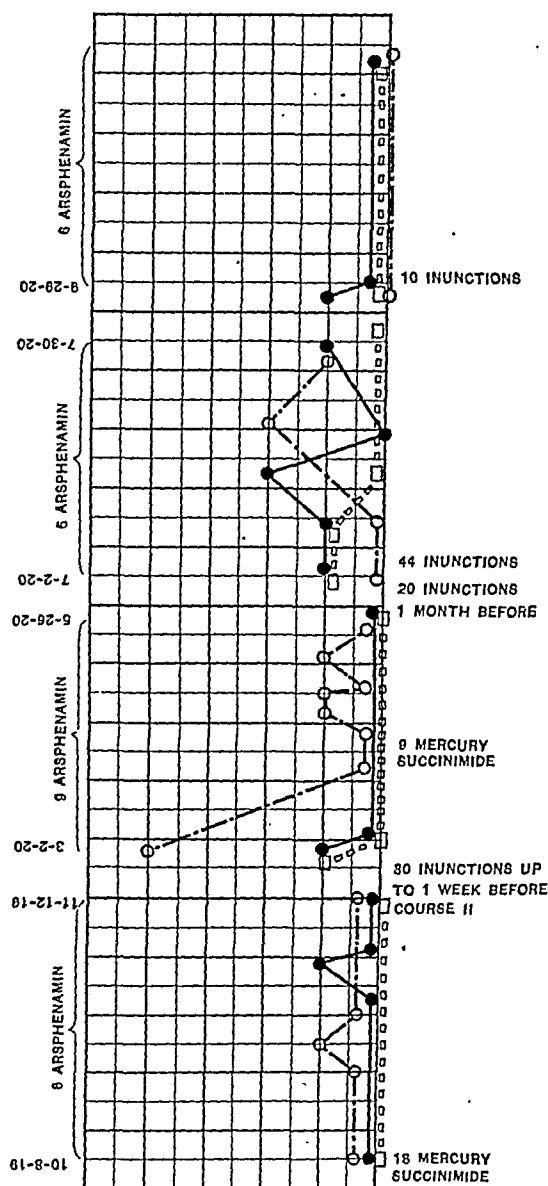


FIG. 2.—Case A291062. Return of the kidney to normal without treatment for nephrosis.

cases, and to decrease in 26 per cent. Albumen tended to increase in 40 per cent, and to decrease in 13 per cent. Pus tended to increase in 13 per cent and to decrease in 16 per cent. These data, in general, seem to indicate an increasing reactivity on the part of the kidney as treatment is prolonged. A few cases dis-

played this increasing reactivity to mercury in particular, in a striking manner (Fig. 9). In 1 case, after several years of treatment, the kidney reacted sharply to a single injection of mercury salicylate. The relative reactivity of the kidney to mercury and arsphenamine will be discussed later.

The question naturally arises as to whether the irritation results in permanent or temporary damage to the kidney. The answer has been intimated in part by the fact that in no case throughout

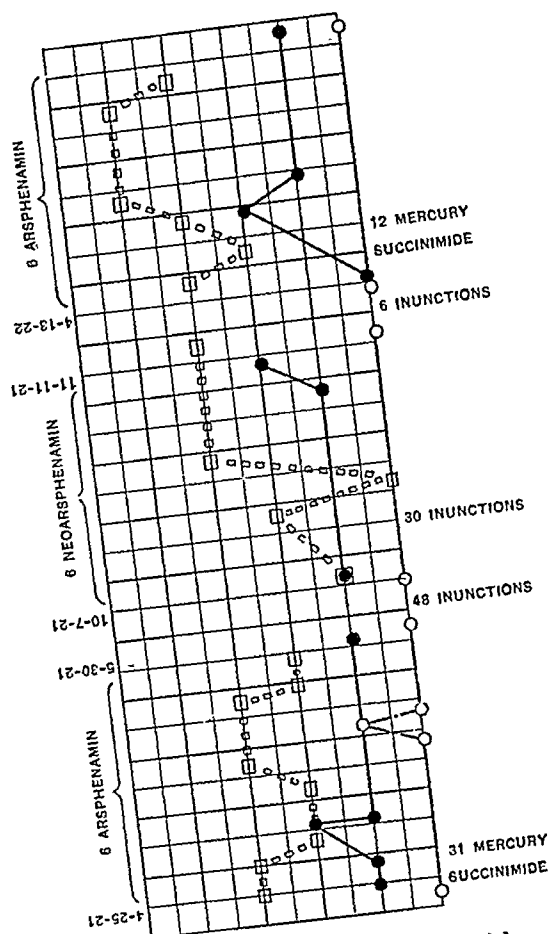


FIG. 3.—Case A345695. "Neurogenous" or cord bladder with very few casts, under antisypilitic treatment.

its course was there serious renal impairment, as indicated by blood-urea determinations and by the phenolsulphonephthalein excreting power; also that no clinical evidence of severe intoxications was noted, such as edema, headache, nausea or impending uremia. The slight abnormality induced by prolonged treatment is suggested by the urinary findings. Of the 128 patients whose kidneys were at first normal, and who received 271 courses, only 24 (8 per cent) had casts 2 or above at the end of the individual course. Only 21 (7 per cent) had albumen 2 or above, and only

21 (7 per cent) had pus 2 or above. Thirty-six patients had several courses of treatment and were observed for at least several months after treatment was completed. It was found that 0.7 per cent had casts 2 or above, 0.5 per cent had pus 2 or above and 0.5 per cent had albumen 2 or above. The condition of practically all of these patients, therefore, returned to normal after treatment was stopped. Many of the patients have been observed over a period of two or three years, and it seems reasonably certain that the effect of combined arsphenamine and mercury treatment of patients with normal kidneys is transient rather than permanent, and that while kidneys may become increasingly sensitive to treatment as it progresses, a return to normal is almost certain.

It seems apparent from the foregoing that no one course resulted in serious renal damage, in spite of an increasing tendency to renal reactions, so far as urinary findings show. It was, however,

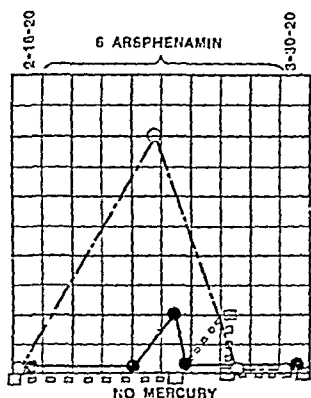


FIG. 4.—Case A304329. Renal flare-up during arsphenamine administration.

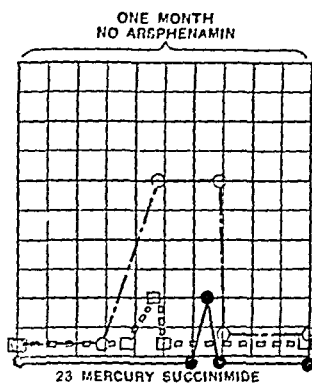


FIG. 5.—Case A387640. Renal flare-up during mercury administration.

thought advisable to ascertain if there was less tendency for the urine to return to normal, as patients were given repeated courses of treatment. It was found that the casts remained 2 or above in 9 per cent, albumen 2 or above in 6 per cent, and pus 2 or above in 3 per cent of patients receiving one course. Of patients receiving two courses, 12 per cent ended with casts 2 or above; 11 per cent, albumen 2 or above; 5 per cent, pus 2 or above. Of the patients receiving three courses, 8 per cent ended with casts 2 or above, 5 per cent with albumen 2 or above and 9 per cent with pus 2 or above. Of those receiving four courses, 6 per cent ended with casts 2 or above, none with albumen 2 or above and none with pus 2 or above.

It is probable, therefore, that, provided a sufficient rest interval is allowed, namely one to three months, the kidneys will return to normal after at least four courses of treatment. The fact that a patient has had a renal flare-up from treatment during one

course is no reason why second, third and fourth courses should not be given, if properly managed.

The patients reviewed thus far have been treated by the combined administration of arsphenamine and mercury. The use of arsphenamine and mercury, as employed in the treatment of syphilis, has been seen to result in a form of renal irritation which can be expected to disappear rapidly. It is of interest to note just what part each drug plays in the irritation of the kidney.

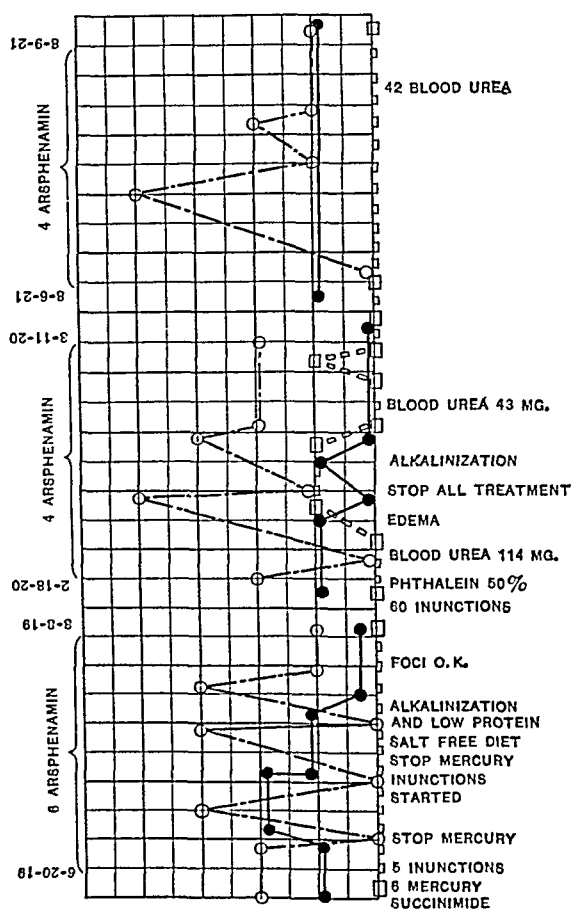


FIG. 6.—Case A273325. Toxic nephrosis superimposed on chronic nephritis.

In a study of the pathological changes produced in the kidney of animals by arsphenamine and mercury, Kolmer and Lucke found that the greatest damage is done to the epithelium of the tubules, consisting, chiefly, of cloudy swelling and fatty degeneration of the cells, with shrinking or dilatation of the tubules, which were often occluded by casts, erythrocytes and leukocytes. Changes were most marked in the convoluted tubules, but were also found in the collecting tubules. These authors note also, to a less extent, distention or shrinkage of the glomeruli, and certain evidence of interstitial new-cell formations. Menten used mercuric chloride

in rabbits and found the chief pathological lesion to consist in degenerations of the epithelial cells of the convoluted tubules. These changes occurred in a remarkably short time, in some cases in from three to five minutes after injections.

Béinhauer gave calomel to a series of patients, and found that mercury could be detected in the urine up to the fifth or sixth day after administration. He also found that the urine contained casts and albumen up to the fourth day after administration; the urine soon returned to normal, and he concluded that the damage was transient.

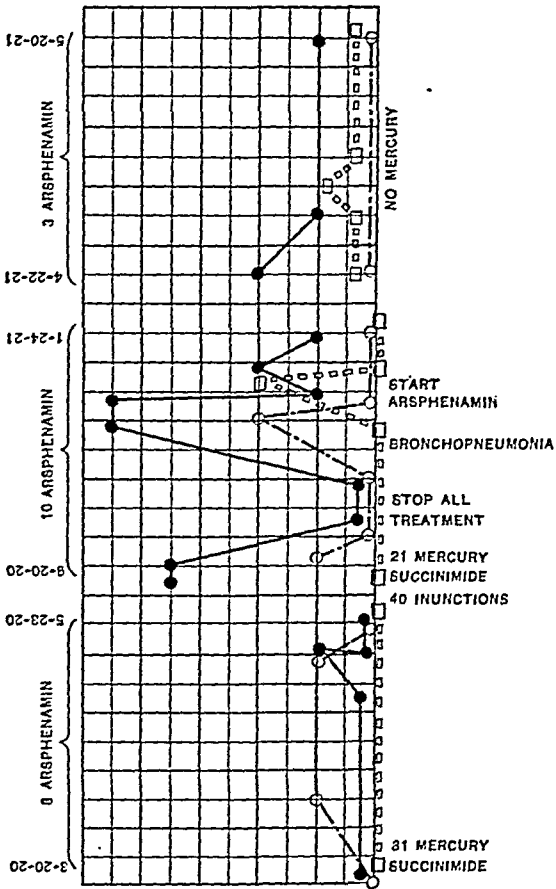


FIG. 7.—Case A307472. Effect on the kidney of intercurrent infection while under treatment.

While the literature seems to emphasize the greater tendency of mercury to produce renal irritation, as compared with arsphenamine, certain authors have pointed out the irritating effect of arsphenamine on the kidney. Elliott and Todd seem to conclude, from a study of 25 cases treated with arsphenamine, that there is impairment of renal function, as indicated by the phenol-sulphonephthalein output and blood-urea findings, yet their data show so little reduction in function as to make this point rather

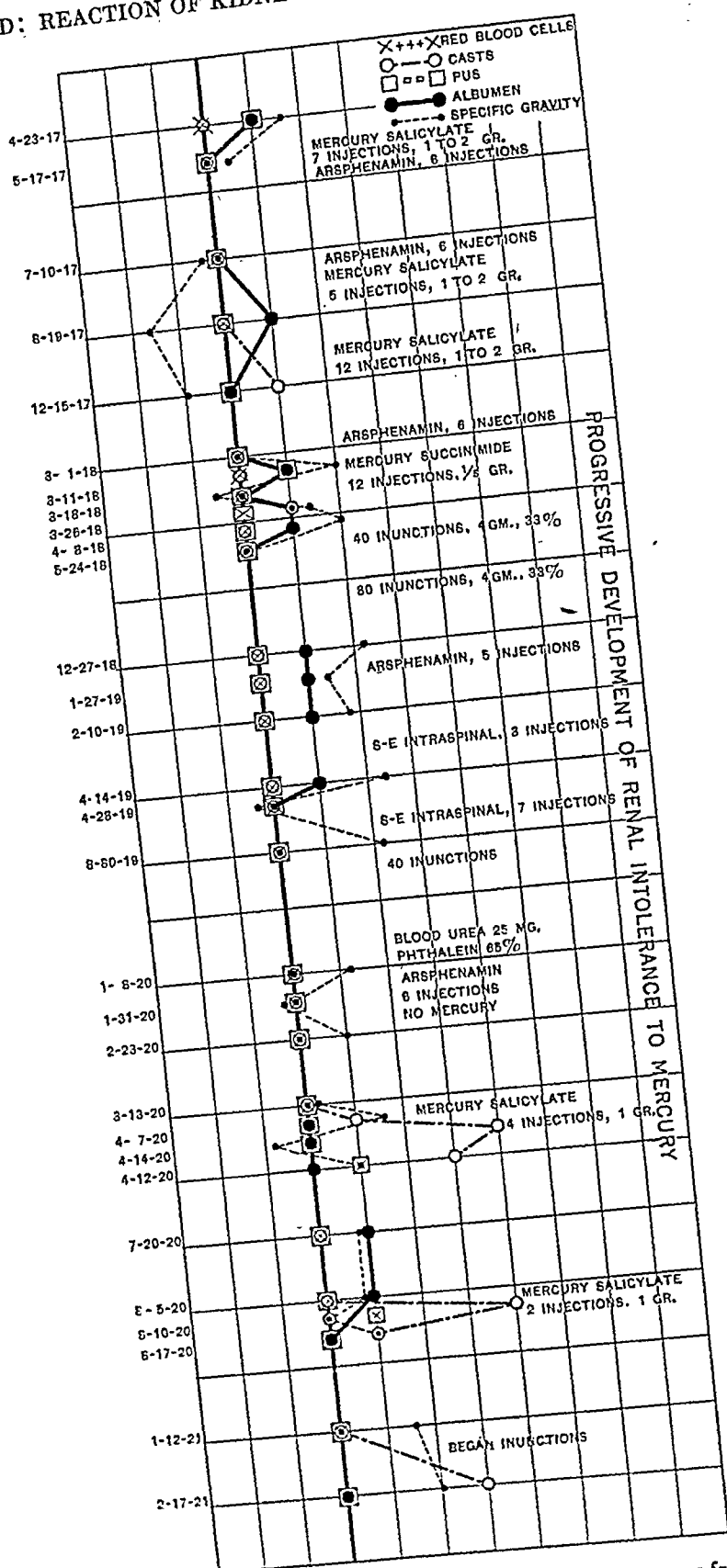


FIG. 8.—Case A288578. Good effects of withdrawing mercury from treatment.

doubtful. Mohr has reported 3 cases in which he believes severe renal injury resulted from the administration of arsphenamine. Schlasberg has reported 27 cases in which casts and albumen

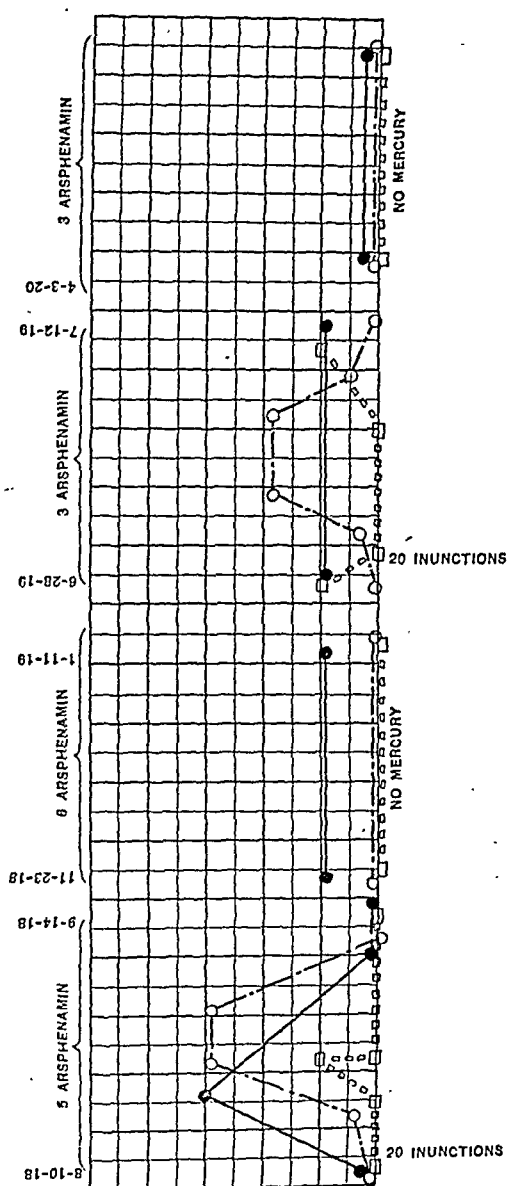


FIG. 9.—Case A160404. Gradual development of an extreme grade of intolerance to mercury in a patient under observation for four years. From an excellent tolerance of intensive mercurialization his ability to withstand mercury fell to the point where he could not even take small inunctions, though the urine was entirely normal between times.

appeared in the urine after arsphenamine was given, which led him to believe that the matter is of importance. Wechselmann has reported several cases of definite renal irritation following the administration of arsphenamine.

The pathological changes in the kidney, under mercury and arsphenamine, seem to fall into the group of nephrosis, as defined by Volhard and Fahr's classification, or to correspond to what Delafield calls "degeneration of the kidney." The urinary findings consist of the presence of casts, albumen, pus, and occasionally erythrocytes. The renal function is unimpaired, and edema, headache, nausea, diarrhea and coma occur only in advanced cases.

In order to determine the relative parts played by arsphenamine and mercury in the renal reactions in this series, two groups of patients were studied, who were treated by one or the other of these drugs. Eighty-four patients with renal irritation, who received arsphenamine only, had normal urine at the outset. Of these, 8 per cent developed casts 2 or above, 7 per cent developed albumen 2 or above, and 9 per cent developed pus 2 or above. Fig. 4 illustrates a rather marked flare-up, which may occur with arsphenamine only. On the other hand, in a series of 28 patients with renal irritation, who had received only mercury, it was found that 32 per cent developed casts 2 or above; 21 per cent, albumen 2 or above; 18 per cent, pus 2 or above. It is apparent that marked renal irritation is decidedly more common in patients under mercurial treatment alone than under arsphenamine treatment alone. Fig. 5 illustrates a renal flare-up which may occur under mercurial treatment. While it may be unwise to grade toxic nephrosis on too mathematical a basis, it will be of interest to note that the average grade of renal reaction, as measured by the urine, in patients who received both mercury and arsphenamine, is approximately equal to the average combined reaction caused by mercury and arsphenamine given separately, particularly with regard to casts, which seem to be the most sensitive indicator of renal irritation. There was a definite increase in casts in 46 per cent of cases under combined treatment, whereas the sum of the increased casts in cases under arsphenamine and mercury separately was 40 per cent.

No appreciable difference was noted in the rapidity of action on the urine between intramuscular mercury succinimide and mercurial inunctions. About 70 per cent of the patients treated only with mercury received the succinimide, while 30 per cent had inunctions. Examples were found frequently of rapid development of urinary abnormalities under both modes of administration.

The time required for the kidney to return to normal after the administration of mercury was studied in a series of 83 cases. The patients received more than one course of treatment and were put on mercurial inunctions during the rest period between courses. It was found that when a period of one month or longer had intervened since the mercury was stopped only 20 per cent of patients had casts, albumen or pus, whereas if the rest period had been only one or two weeks 80 per cent had slight urinary changes.

It seems, therefore, that the kidney, under non-cumulative mercurial treatment, practically recovers completely from intensive mercurialization within a month after the drug is stopped.

Up to this point, as nearly as could be determined, all the patients studied had normal kidneys at the beginning of treatment. Several groups of patients with abnormal kidneys were next studied with reference to their behavior under treatment for syphilis. In the cord-bladder group there were 31 patients who had had a cystoscopic diagnosis of tabetic or neurogenous bladder. Sixty-nine individual courses were given to the 31 patients; all were treated with mercury and arsphenamine simultaneously. All had a great deal of pus and albumen in the urine, because of the condition of their bladders. However, a remarkably small number developed casts while under treatment. In 42 of the 69 courses no casts were found. Twenty-one patients had casts 1 only, 5 had casts 2 and 1 had casts 3. Several explanations for this apparent absence of irritation were considered: (1) It was thought that the urinary tract, being more or less severely infected, was, as it were, rendered immune to slight renal irritation, such as is produced by treatment for syphilis. (2) It was thought that treatment might have been less intensive and more cautiously conducted with respect to dosage and intervals because of the infection of the bladder; while this was true in certain instances, yet on the average the treatment was quite comparable in intensity to that given the normal patient. (3) It was thought that the casts might have undergone autolysis in the stagnant infected bladders. It is possible that this last factor is largely responsible for the apparent immunity of the patient with a tabetic bladder to the toxic nephrosis of treatment for syphilis. However, this does not seem entirely to explain the situation. It will be noted that quite a proportion of patients had casts in the urine, and a few had a very considerable amount. One patient with a large number of casts in the urine had a cord bladder. Fig. 3 illustrates the case of a man, aged sixty years, with a cord bladder, who had intensive treatment and very little increase in casts. The urines of both patients were twenty-four-hour specimens, and were examined under the same conditions as those of the normal patients.

The second group of 65 patients receiving 100 courses included patients who had renal lesions to start with; those with tabetic bladders and pyelonephritis were excluded. These patients were treated simultaneously with arsphenamine and mercury. As nearly as the pathological conditions could be classified they were chronic nephritis without hypertension, 15 per cent; focal nephritis, 45 per cent; chronic nephritis with arteriosclerosis and hypertension, 33 per cent; nephrosis, 3 per cent; nephrolithiasis, 3 per cent. Taken as a group, the urines before treatment revealed an average of casts 2 or above in 6 per cent, albumen 2 or above in 13 per cent, and pus

2 or above in 12 per cent. During treatment there were casts 2 or above in 64 per cent, albumen 2 or above in 30 per cent, and pus 2 or above in 42 per cent. At the end of treatment there were casts 2 or above in 11 per cent, albumen 2 or above in 7 per cent, and pus 2 or above in 15 per cent. It would appear that in this group, according to urinary findings, the reaction to mercury and arsphenamine was more severe than in the group of normal cases. However, the kidneys returned practically to the condition present before treatment was started. In other words, a toxic nephrosis had been superimposed on abnormal kidneys, and when the nephrosis passed off, the kidneys were left in practically their original condition, thus indicating that because a patient with syphilis happens to have a damaged kidney, treatment for syphilis is not necessarily contraindicated.

Fig. 6 is an example of nephrosis superimposed on nephritis with its end-result. This case was diagnosed clinically as chronic nephritis. It will be noted that treatment was fairly intensive, and that there was an increase of casts and pus cells and a few erythrocytes, together with temporary increase in the blood urea. The urinary findings eventually, however, returned approximately to the former status and the blood urea was lowered. Wilder believes that nephrosis had been superimposed on a chronic nephritis, but that no damage had been done.

The influence of age on renal irritability was next considered. Of the patients starting with normal kidneys 62 per cent were more than forty-five years of age. While these patients were under treatment casts 2 or above developed in 53 per cent, albumen 2 or above developed in 15 per cent, and pus 2 or above developed in 12 per cent. It will be noted that while the increase of casts is slightly greater in this group than in the entire series, the increase of albumen and pus is slightly less. It is probably fair to conclude that no appreciable difference in reaction was noted in the group of patients more than forty-five years of age, as compared with the entire group. While the end-results, so far as the kidney is concerned, are quite satisfactory after treatment for syphilis, as employed in the Mayo Clinic, the impression should not be given that the management of these cases may be conducted carelessly, nor should it be inferred that any form of treatment for syphilis may be used with similar results. The opinions expressed in this paper apply only to the use of arsphenamine and mercury, as outlined, and to the management of cases, as carried out in the Section on Dermatology and Syphilology of the Mayo Clinic.

Treatment of Nephrosis. In order to determine the effective uses of collateral medical measures employed in the Section on Dermatology and Syphilology in controlling renal disturbances of patients with syphilis under mercury and arsphenamine treatment, the following summary was made: The collateral treatment consists

of: (1) Alkalization, that is, the daily administration by mouth of a powder containing 1 dram each of sodium citrate and potassium bitartrate; (2) placing the patient on a low-protein, salt-free diet; (3) removing all detectable foci of infection, such as infected teeth or septic tonsils; (4) stopping the use of mercury temporarily. One or several of these measures were used in most cases. A series of 219 courses of treatment were studied. All of the patients had normal urine to start with and all had very definitely abnormal urine during treatment. Twenty-five of the 180 patients improved with alkalization alone; none with low-protein, salt-free diet; 27 with the removal of septic foci; 7 by combining alkalization and low-protein, salt-free diet; 5 by combining alkalization and the removal of foci; none by low-protein, salt-free diet and removal of foci; 12 by removing foci, alkalization and low-protein, salt-free diet; 19 by alkalization, removal of foci, low-protein, salt-free diet and stopping mercury temporarily; 36 by stopping mercury alone; 49 returned to normal without treatment, the mercury and arsphenamine being continued. Thirty-nine patients did not improve by similar measures; 8 had alkalization alone; none had low-protein, salt-free diet; 7 had foci removed; 1 had a combination of low-protein, salt-free diet and alkalization; 4 had foci removed and alkalization; none had foci removed and low-protein, salt-free diet; none had low-protein, salt-free diet, alkalization and foci removed; 4 had low-protein, salt-free diet, alkalization, foci removed and mercury stopped; 2 had mercury stopped only, 13 did not have treatment.

Because of the various combinations of treatment in individual cases, it is difficult to draw conclusions with regard to the value of any particular measure. It is significant, however, to note that of the patients who improved promptly after a flare-up, 53 per cent had some combination of these therapeutic measures, while 47 per cent had no treatment, or only withdrawal of the mercury. Of those who did not show prompt improvement, 62 per cent had had some of the treatments mentioned and 38 per cent had not. These data seem to show that ordinarily the irritation of the kidney which occurs under treatment for syphilis has a marked tendency spontaneously to return to normal, regardless of treatment. While the measures employed seemed to hasten the process in some instances, yet the effect cannot be said to be very striking. Withdrawal of mercury seemed to be the most important single procedure in relieving the kidney of its added burden.

Several examples may be given of the peculiar situations which arise in the management of patients with renal disorders. One patient (Case A292019) with nephritis, who was very sensitive to the drugs administered, made little if any response to therapeutic measures, and eventually the urine returned almost to normal. Fig. 8 illustrates the good effect obtained by withdrawing mercury. In

the first and third courses, when mercury was given, there was definite evidence of renal irritation, while in second and fourth courses, when mercury was not given, the urine remained practically normal. In another case (A320763), the foci of infection were not removed, yet the urine returned to normal. In one case (A183849) in which the foci of infection were cleared up, there was a definite kidney flare-up later in the treatment. Fig. 1 seems to illustrate the beneficial effects of alkalization, low-protein, salt-free diet and removal of foci. Fig. 2 illustrates a case which returned to normal without treatment. That intercurrent infections may increase the irritability of the kidney has often been noted. Fig. 7 illustrates the case of a patient who developed bronchopneumonia while under treatment. The irritability of the kidney is evident, although the eventual outcome is satisfactory.

Conclusions. 1. Reaction of the kidney to mercury and arsphenamine, as employed in the treatment for syphilis consists in what, according to Volhard and Fahr's classification, is nephrosis. The pathological condition is essentially a more or less marked degeneration of the epithelium of the renal tubules.

2. Urinary findings consist of hyaline or granular casts, albumen, pus and erythrocytes.

3. Casts are the most sensitive indicator of renal irritation. They are usually first to appear and are more numerous than albumen or pus.

4. Erythrocytes should be rarely encountered in the urine of patients with normal kidneys under treatment for syphilis.

5. Lowering of the phenolsulphonephthalein excreting power of the kidney and elevation of urea in the blood are rarely encountered under treatment for syphilis.

6. In no case observed was renal damage sufficient to cause edema, headaches, nausea, impending coma, or other signs or symptoms of severe renal damage.

7. Practically all patients who have had a characteristic renal reaction to treatment, return to normal again if given sufficient time.

8. Arsphenamine alone, when properly prepared and given, causes only slight renal irritation.

9. Neoarsphenamine appears to cause less reaction than arsphenamine.

10. Mercury is by far the most important factor in renal irritation under treatment.

11. Whether mercurial inunctions or intramuscular injections of mercury succinimide are given, seems to make little difference in the time of appearance or extent of renal irritation.

12. The renal irritation resulting from combined arsphenamine and mercury treatment is practically equivalent to the sum of that produced by the two drugs given separately.

13. Approximately one month is the proper time to allow for the urine to return to normal after stopping non-cumulative mercurial treatment for syphilis.

14. Acute syphilitic nephritis must not be confused with acute nephritis in a patient with syphilis. The condition may so closely simulate true syphilitic nephritis that a therapeutic test with arsphenamine is the only means of reaching a diagnosis.

15. Patients with cord bladders, under treatment for syphilis, have very few casts in the urine. This may be due, in part, to disintegration of the casts in bladders with residual urine, but several facts seem to indicate that the kidneys of such patients are really less reactive than the normal ones, and stand intensive treatment fairly well.

16. Patients who have damaged kidneys, as evidenced by chronic nephritis, nephrosis, focal nephritis and so forth, show a higher degree of reactivity to treatment than normal patients, but recovery seems to be quite as satisfactory.

17. Intercurrent infections, such as bronchitis or bronchopneumonia occurring in a patient under treatment, may cause an additional flare-up, but such a complication need not contraindicate future treatment from the renal standpoint.

18. There is a certain tendency for more severe reactions to occur as treatment progresses.

19. If sufficient time for recuperation is allowed repeated courses of treatment may be given, at least up to three or four, without causing significant renal damage.

20. Age is not, as such, a contraindication to treatment for syphilis.

21. There is a marked tendency for spontaneous recovery from the renal irritation, even in the face of continued administration of the drugs.

22. General measures which may influence the toxic nephrosis, such as removal of foci of infection, alkalization of the patient and low-protein, salt-free diet, may be of some value in certain cases, although the results are not uniform nor striking.

23. Stopping the administration of mercury is the most effective means of bringing the urine back to normal. In view of the good prognosis with regard to the nephrosis, the mercury should not be stopped too frequently; the rest periods should be sufficient to control the situation.

BIBLIOGRAPHY.

1. Beinhauer, L. G.: Effect of Therapeutic Doses of Mercury on Kidneys and Duration of its Excretion, *AM. JOUR. MED. SCI.*, 1920, 159, 897.
2. Cole, H. N.: Acute Syphilis of the Kidney, *Am. Jour. Syph.*, 1920, 4, 46.
3. Day, H. B.: A Case of Syphilitic Nephritis, *Lancet*, 1920, 1, 1009.
4. Elliott, J. A., and Todd, L. C.: Acute Syphilitic Nephritis, *Arch. Dermat. and Syph.*, 1921, 3, 634.
5. Elliott, J. A., and Todd, L. C.: Effects of Arsphenamine on Renal Function in Syphilitic Patients, *Arch. Dermat. and Syph.*, 1920, 2, 699.

6. Epstein, A. A.: Clinical Types of Chronic Parenchymatous Nephritis; Their Treatment and Results, *Med. Clin. North America*, 1920, 4, 145.
7. Fischer, M.: The Classification and Treatment of the Nephritides, *Pennsylvania Med. Jour.*, 1918, 21, 236.
8. Floyd, R.: Two Classifications of Bright's Disease, *Med. Rec.*, 1921, 99, 558.
9. Fournier, A.: *Traité de la syphilis*, Paris, 1906, 1, 734.
10. Hoffman, E.: Ueber akute syphilitische Nierenentzündung in der Frühperiode (Nephritis syphilitica akute praecox), *Deutsch. med. Wchnschr.*, 1913, 39, 353.
11. Karvonen, J. J.: Acute Syphilitic Nephritis, *Dermat. Ztschr.*, 1900, 7, 37, 183, 460, 770, 903.
12. Kolischer, G.: Nephritis, Nephrosis and Pyelitis, *Urol. and Cutan. Rev.*, 1921, 25, 203.
13. Kolmer, J. A., and Lucke, B.: Study of the Histological Changes Produced Experimentally in Rabbits by Mercurial Compounds, *Dermat. and Syph.*, 1921, 3, 531.
14. Kolmer, J. A., and Lucke, B.: A Study of the Histological Changes Produced by Arsphenamine and Neoarsphenamine, *Arch. Dermat. and Syph.*, 1921, 3, 515.
15. Menten, M. L.: Pathological Lesions Produced in Kidney by Small Doses of Mercuric Chloride, *Jour. Med. Res.*, 1922, 43, 5.
16. Mohr, R.: Ueber Nierenschädigungen durch Salvarsan, *Med. Klin.*, 1911, 7, 613.
17. Munk, F.: Klinische Diagnostik der degenerativen Nierenerkrankungen, *Ztschr. f. klin. Med.*, 1913, 78, 1.
18. Musser, J. H., and Kelly, A. O. J.: Practical Treatment, Philadelphia and London, W. B. Saunders, 1917, 4, 755.
19. Schlasberg, H. I.: Salvarsanets inverkan på njurarna vid intravenösa injektioner, *Nord. med. Ark.*, 1912, 45, 1.
20. Silverman, D. N.: Nephritis in Syphilis, *New Orleans Med. and Surg. Jour.*, 1921, 73, 415.
21. Stengel, A., and Austin, H.: Syphilitic Nephritis, *AM. JOUR. MED. SCI.*, 1915, 149, 12.
22. Stokes, J. H.: Acute Syphilitic Nephritis from the Standpoint of Diagnosis and Salvarsan Treatment, *Jour. Am. Med. Assn.*, 1916, 66, 1191.
23. Stokes, J. H.: Syphilitic (?) Parenchymatous Nephritis, *Am. Jour. Syph.*, 1920, 4, 547.
24. Symmers, D.: Acute Syphilitic Glomerulonephritis, *Interstate Med. Jour.*, 1917, 24, 1010.
25. Waldorp, C. P., and Behr, O.: Syphilitic Disease of the Kidneys, *Semana méd.*; Abstract, *Jour. Am. Med. Assn.*, 1922, 78, 549.
26. Wechselmann, W.: Kritische Bemerkungen zur Pathogenese eines "Salvarsantodesfalles," *München. med. Wchnschr.*, 1914, 2, 1845.
27. Weisfelt, W. A.: Syphilitic Disease of the Kidneys, *Nederl. Tijdschr. v. Geneesk.*, 1921, 1, 3073; Abstract, *Jour. Am. Med. Assn.*, 1921, 77, 658.
28. Wilder, R. M.: Personal communication.

OBSERVATIONS UPON THE GROWTH AND LENGTH OF THE HUMAN INTESTINE.*

By JOHN BRYANT, M.D.,
BOSTON.

Introduction. "The lectures on 'The Anatomy of the Intestinal Canal and Peritoneum in Man,' delivered last week by Mr. Treves

* Read before the annual meeting of the American Gastro-enterological Association, Atlantic City, April, 1923. Original data for this article obtained in 1912-1914 through the courtesy of Profs. Pick and von Hansemann, of Berlin, Prof. Frankel, of Hamburg, and the students then working in their pathological institutes.

at the Royal College of Surgeons, demonstrate the absurdity of a prevalent idea that human anatomy is a worked-out science. This notion is not only an error, but an evil, like all other fallacies connected with scientific questions.

"The brilliant results of microscopical research have decidedly seduced many scientific anatomists from their old enthusiasm for naked-eye dissection. The experience of Mr. Treves has shown that much remains to be done, and always will remain to be done in the dissecting-room, without the aid of any lens, excepting those which are necessary, in the form of a pair of spectacles, should the dissector suffer from a disorder of accommodation.

"It cannot be doubted, however, that the great evil involved in the belief that the end of human anatomy has been reached, is an excessive confidence in text-books on the subject. It should never be forgotten that a text-book is essentially transitory in character, being a summary of knowledge brought down to the date of its publication, and prepared in a form suitable for instruction. Yet the assertions of text-books are too often held to be sacred traditions.

"The account of the cecum as given in works of anatomy would appear to be very ancient. It can be traced back, by the lecturer, from book to book, through many literary generations; and throughout its long history it seems to have undergone little or no alteration. It is one of those descriptions, we are reminded, that form a real anatomical property, and that descend from one author to another with the precision of entail. A more fertile source of error could hardly be conceived; yet we are all aware that similar traditions concerning every part of the human body are handed down from text-book to text-book, while their incorrectness is overlooked by thousands of good observers and patient dissectors. All of us are apt to forget that, in science, nothing written must be taken for granted."

Although the above paragraphs were written in 1885, by the editor¹⁰ of the *British Medical Journal*, they apply equally well today with regard to many persisting anatomical properties and text-book traditions. In fact, more than a generation after the original lectures upon "The Anatomy of the Intestinal Canal and Peritoneum in Man" were delivered by Treves, many of Treves' own statements concerning the growth and length of the intestine, continue to be handed on from text-book to text-book; yet proof is available that some of these statements themselves fall within the classification of "anatomical properties."

The objects of this paper are as follows: To review some of the findings of previous investigators; to correct some of their statements which cannot be verified; and to present for consideration additional data upon the growth and length of the human intestine not hitherto available, because based upon original material until now unreported.

Literature. Interest in the general subject of intestinal length is by no means of recent origin, as witness the writings of Spigelius,²⁰

who in 1632 concluded that the ratio of body length to intestinal length was about 1 to 6. Many later writers have concerned themselves with this subject. Thus Meckel¹⁷ in 1817 established the variability of the relationship between fetal body length and fetal intestinal length; he correctly stated that although in the early fetus the intestine is relatively short, the full term fetus has acquired an intestinal length even greater in relation to body length than is found at any subsequent period of life.

Later in the last century, Crampe,⁵ Custor,⁶ Cuvier⁷ and Werner,²⁴ studied exhaustively the question of intestinal length in the lower animals, and their researches in comparative anatomy doubtless may have served as one point of departure for recent communications, as by Bean,² Bryant,⁴ Swaim²¹ and others, upon a possible existence of contrasting body types in the human.

Frequent references exist in the literature, to the possibility of a correlation between intestinal length and race or nationality, this idea being perhaps based upon a reported apparent correlation in the lower animals between intestinal length and the degree of digestibility of the habitual foods of these animals. These attempts at correlating intestinal length with racial characteristics have not in general yielded definite results, doubtless because the cases studied all came from not sufficiently widely separated parts of Europe. But two articles by Deakin,⁸ and Lamb,¹⁶ suggest that some such racial factor in intestinal length may in fact exist. Thus, Deakin reporting on the length of the intestine in India, recorded an average distinctly longer than the accepted European average; and Lamb, reporting upon the length of the intestine of American negroes, recorded an even higher average, with a maximum of 40 feet for the length of the small intestine alone.

The two papers which the writer considers most deserving of attention, are those by Treves²³ and by Dreike.⁹ They are deserving of attention for very different reasons. Dreike has presented the most careful study of intestinal length to which the writer has had access. The article by Treves on the other hand, bases statements in regard to intestinal length upon a minimum of scientific information other than his own frequently unsupported assertion: yet because this article by Treves is one of the best known upon the subject in the English language, and because it continues to be so widely used as a basis for reference in the text-books of today, it must be seriously considered. It is to be remembered that Treves devotes only a few of his opening paragraphs to the subject of intestinal length, and it is to the subject matter of these opening paragraphs only, that reference is here made.

It will be seen from a consideration of Table A, that with the exception of the present work by the author, Dreike has investigated a distinctly larger number of cases than any one working in this field; in one respect, the total number of children examined,

TABLE A.—OUTLINE OF AUTHOR'S FINDING AND OF RECENT LITERATURE.
(*Intestinal Lengths Recorded in Feet and Inches.*)

Authors.	Date.	Total cases.	No. of obs.	Age.	Sex.	Small intestine.			Colon.			Total intestinal length.			
						Min.	Average.	Max.	Min.	Average.	Max.	Min.	Average.	Max.	
Bryant	1923	242	45	Total	Both	10'	20'6"	28'4"	3'4"	5'2"	10'10"	13'4"	25'8"	39'2"	
			37	Child	Both	15'	21'9"	26'8"	3'8"	5'4"	9'2"	18'8"	27'1"	35'10"	
			160	Adult	M.	13'4"	19'3"	25'	3'4"	4'6"	6'8"	16'8"	23'9"	31'8"	
			27	Adult	F.										
Dreiko	1895	171	17	Adult	Both										
			104	Child	Both										
			67	Adult	Both										
			27	Adult	M.	13'10"	20'9"	33'3"	3'8"	5'3"	7'4"	17'6"	26'	40'7"	
Robinson	1895	113	23	Adult	F.	11'2"	17'3"	28'2"	3'8"	5'	6'4"	14'10"	22'3"	34'6"	
			87	Adult	M.	12'6"	23'3"	33'	3'8"	5'	6'4"	14'10"	22'3"	34'6"	
			26	Adult	F.	11'	18'	29'	3'8"	5'	6'4"	14'10"	22'3"	34'6"	
			..	Adult	M.	15'6"	22'6"	31'10"	3'3"	4'8"	6'6"	18'9"	27'2"	38'4"	
Troves	1885	100	..	Adult	F.	18'10"	23'	29'4"	3'3"	4'6"	6'6"	22'1"	27'6"	35'10"	
			100	Adult	Both	15'	20'	25'	3'3"	4'6"	6'6"	22'1"	27'6"	35'10"	
			100	Child	Both										
			100	Adult	Both										
Bean	1916	100	22	Child	Both										
			78	Adult	Both	15'	23'8"	40'	5'	5'3"	6'	20'	28'11"	46'	
			48	Adult	M.	16'	25'	40'	4'	5'6"	6'	20'	30'6"	46'	
			..	Adult	F.	15'8"	22'2"	27'4"	3'	4'6"	6'	20'	30'6"	46'	
Lamb	1893	48	..	Adult	Both	15'8"	20'3"	24'8"	3'	4'6"	6'11"	18'8"	26'8"	33'4"	
			..	Adult	F.	15'1"	20'3"	24'8"	3'	4'6"	6'11"	18'8"	26'8"	33'4"	
			39	Adult (thin)	..	10'6"	19'3"	25'10"	3'8"	5'	8'5"	19'1"	24'9"	31'7"	
			29	Adult (fat)	..	10'6"	19'3"	25'10"	3'8"	5'	8'5"	19'1"	24'9"	31'7"	
Rolsenn	1890	Adult	..										
			..	Adult	..										
			..	Adult	..										
			..	Adult	..										
Swain	1912	39	10	Adult (thin)	..	10'6"	19'3"	25'10"	3'8"	5'	8'5"	14'2"	24'3"	34'3"	
			29	Adult (fat)	..	10'6"	19'3"	25'10"	3'8"	5'	8'5"	14'2"	24'3"	34'3"	
			..	Adult	..										
			..	Adult	..										

he has examined more cases than any one else. He seems however like some of his predecessors to have fallen into error, by devoting an undue amount of attention to mere methods of measurement, neglecting meanwhile to limit as nearly as possible to one, the number of variables in any given group of cases under consideration. The number of cases in each of his groups may be adequate, but when he attempts to determine for instance the possible effects of inflammation of the intestines upon intestinal length, he must compare the measurements from this abnormal group with the findings of a so-called normal group; one fallacy is that he uses as normals, figures arrived at only after including wide variations in height, age, etc. In a word, there is little evidence that he took sufficient care to establish accurate normals with which to compare his subsequent findings.

Summarizing his own findings and comparing them with those of his predecessors, Dreike⁸ concluded that in the child the question of sex made no difference in regard to intestinal length. He was correct in agreeing with Rolssenn,¹⁹ that the adult male intestine is longer than that of the adult female. Dreike reported that Meckel,¹⁷ Crampe,⁵ Beneke,³ and Frolowsky¹¹ agreed with him that in the child (as is the fact) the intestine is relatively longer than in the adult, whereas Huschke,¹⁴ Henle,¹² Henning¹³ and Tarenetsky²² disagreed. But Dreike disagreed with Meckel (and rightly so), in finding with Frolowsky that the colon is longer (in relation to the small intestine) in the adult than in the child. After concluding that the question of race or nationality was unimportant, Dreike found himself (but this time incorrectly), in agreement with Beneke, Tarenetsky, and Kretschmann¹⁵ with regard to the existence of a short intestinal length in subjects tuberculous or predisposed to tuberculosis.

A critical examination of the scientific basis for many of the assertions made by Treves²³ concerning the growth and length of the intestine, does not reveal adequate authority for several of his statements. Although his total material, "100 fresh bodies," is stated, there is no indication of the actual numbers of males and females constituting this total. Treves states that he "derived considerable information from the dissection of a number of fetuses of various ages," but he neglected to say how many fetuses he dissected, or whether they were included in his total of "100 fresh bodies" above referred to. He gives the length of the small intestine for the adult male between the ages of twenty and fifty years, but does not indicate the number of cases upon which his figures are based. For the adult female, not even the age limits are given; merely the intestinal length is stated. This is apparently all the evidence necessary to convince Treves himself that "the length of the bowel is independent in the adult at least, of age, of height, and of weight; nor is the ratio between the measurements of the small and large intestine constant." From this small beginning,

he thinks "therefore that it must be allowed that the differences in the length of the intestine—differences that, in the lesser bowel may actually reach to no less than 15 feet—depend upon physiological and not upon morphological data."

With regard to the growth of the bowel in infancy, Treves makes numerous categorical statements which rest upon no adequate discoverable scientific foundation. Thus he declares that "in the fetus at full term, the length of the intestine and especially of the colon, is singularly constant."

My observations indicate that this statement is absolutely incorrect; there exists at birth as at all later periods in life, a total variation in intestinal length averaging 100 per cent for any grouping of cases which one may devise in either or both sexes. Furthermore, not only is this 100 per cent variation demonstrable at birth but it is present at least as early as the fifth month of fetal life; also, this 100 per cent variation is demonstrable in both the small intestine and in the colon.

Treves states that the growth of the small intestine is regular for the first two months of extrauterine life, that the growth of the small intestine has no concern with the general growth of the body, and that "all children start life with practically the same length of intestine." He also states that the colon does not increase in length during the four months after birth, after which period growth is steady and regular. Evidence will be presented indicating that these statements also are incorrect. Treves further states that "the absence of growth in the colon for at least the first four months of extrauterine life, is certainly remarkable." This certainly would be remarkable if true. Evidence available, however, does not indicate that it is true.

Treves thereafter leads one to infer that at birth, the sigmoid loop is uniformly of excessive length, and that in the succeeding four months during which there is no growth of the colon, this excessive length of sigmoid flexure universally and progressively becomes reduced by a readjustment which decreases its length in relation to the total length of the colon. The only possible explanation for such sweeping statements is that they must have been based upon an inadequate number of observations. As above stated, these conclusions of Treves would not upon the basis of the scientific support with which they are provided, be worthy of especial notice, were it not for the fact that many of them continue to be copied word for word in our current text-books, to the still further propagation of incorrect "anatomical properties."

Original Data. There are presented herewith, for the most part in tabular form, the results of an examination with regard to intestinal growth and length, of a series of 242 cases of all ages and both sexes. In general, this total is composed of 45 fetal cases, 37 children, and 160 adults. In the fetal group, are 25 males (body length 12.5 to 55 cm.), and 20 females (body length 13 to 52 cm.). In the

group of children there are 20 males between six months and seventeen years of age, and 17 females between two years and sixteen years of age. The adult group is composed of 94 males and 66 females, with body lengths between 140 and 185 cm., and ages between twenty and eighty years.

From these larger groups of cases, numerous smaller groups were selected for purposes of uniformity with respect to body length, age, sex, disease, or any other special subject under consideration. In the accumulation of data, continual effort was directed to the elimination of as many variables as possible, thus reducing the unknown quantities approximately to the one under special review.

In the presence of a total variation in intestinal length averaging 100 per cent, minor variations dependent upon methods of measurement lose some of their theoretical importance. All investigators, even Dreike who measured his intestinal lengths with the greatest care *in situ*, have reported increasing length with successive measurements. Under the conditions offered for my work, it was impossible to obtain the measurements *in situ*. Recourse was therefore had by necessity to the making of all measurements of intestinal length after removal of the intestine from the body. In view of this fact, it is of interest to note that the simple method employed produced results more constant than those of previous workers. Thus Dreike, using the greatest care was unable to prevent progressive increases in intestinal length totaling a meter or more, as a result of repeated measurements of the same intestine. Yet the method employed by the writer yielded when desired as many as three and four consecutive results not varying by a total of more than 10 cm. Whenever an unusually long or short intestine created suspicion of an error in measurement, repeated examination verified the accuracy of the unusual length. The writer's simple method of measurement was the following: After noting that the pathologist had not employed undue traction in removing the intestine from the body, the intestine was allowed to remain in a pan of water for a period of between ten and fifteen minutes, it having been found that this delay was necessary in order to allow the intestine to shrink back to what might be called its normal length following the unavoidable trauma of its removal. The actual measuring was then accomplished by merely running a small portion of the intestine at a time, past a 50 cm. rule, the remainder of the intestine always being submerged in water. In consequence, very little longitudinal strain was necessary and it is perhaps for this reason that it was possible to obtain repeated measurements within such a comparatively small margin of error.

In general, the attempt has been made to present in this paper a very considerable total of original data, in such form as to make them easily and visibly available. For example, there are presented Tables I to IV, the actual measurements of intestinal length found in the fetus and the child.

Table I
Growth and Length of the Human Intestine.
Males - Foetal.

Body length in cm.	Age in Months	Small Intestine Length in Metres										Colon Length in Metres		
		1	2	3	4	5	6	7	8	9	0	1	2	3
12.5	31	.30									.05			
12.5		.31									.05			
13.5		.34												
15.5		.46									.06			
18.5	4	.50									.09			
20.5		.50												
21.0		.52									.10			
22.0	5	.52									.11			
22.5		.50									.14			
23.5	6		1.87	2.90							.45			
24.5			2.15								.57			
25.5	7		1.50								.35			
26.5											.35			
27.5	8			2.50	4.20						.65			
28.5				2.75							.40			
29.5			2.00								.50			
30.5		1.62									.60			
31.5	9		2.50								.53			
32.5			2.50	3.10							.50			
33.5	Birth		2.50								.45			
34.5			2.25								.55			
35.5											.60			
36.5											.60			
37.5											.60			
38.5											.80			
39.5			2.25								.45			

Table IV.
Growth and Length of the Human Intestine.
Female Adolescent.

Body Length in cm	Age	Small Intestine					Colon				
		Length in Metres					Length in Metres				
		1	2	3	4	5	6	7	8	9	0
59	2Y4				3.75						.63
61	6M9					5.10					.75
62	3Y2					5.25					.75
63	1 "				3.25						.61
67	6M9						5.50				.75
70	7 "					4.50					.90
76	2Y4					4.25					1.15
85	4 "			3.00							.68
93	6 "					4.25					1.00
94	3 "						6.00				1.00
102	5 "						5.50				.67
105	5 "				4.00						.75
112	6 "										1.25
112	8 "					4.50					1.00
118	8 "						5.75				1.00
150	14 "						6.00				1.00
160	16 "										
						5.00					

The merest glance at these Tables I to IV, is sufficient to show that whatever the cause of the marked variations in length which occur in the small intestine and colon, they do not first begin to appear at some indefinite period after birth. These variations in length are as obvious at birth as after birth, and they are certainly present as early as the fifth month of intra-uterine life.

From Table I the inference might be drawn that the rate of intestinal growth in the fetus, from the ages of 3.5 to 5 months, is somewhat regular; yet even this apparent regularity in rate of growth of the intestine at this very early age might entirely disappear were a larger number of cases available. It is to be hoped therefore that some future investigator seeking the cause of these demonstrated wide variations in intestinal length, may address himself to a study of intestinal length in the fetus of less than six months of age.

In Tables V to VIII inclusive, there are presented in graphic form the actual variations in length of the small intestine and colon in relation to the four known factors of body length, age, disease and sex.

These variations, figured in percentages, are presented in Tables IX to XVI inclusive.

In Table XVII, is given the percentage increase or decrease in length of the intestine, in relation to the same four factors of body length, age, disease and sex.

The indicated high rate of growth of the intestine in the fetus, is striking. My figures do not support the statement of Bardeen,¹ who, after carefully studying the rate of growth of the intestine in the fetus of less than 1 cm. in length, reports that from a body length of 80 mm. to birth, the rate of growth of both the small intestine and the colon about equal that of the body.

On the other hand, it will be noted that with a 20 per cent increase in body length in the adult (from 150 to 180 cm.), there occurs an increase of only 7.6 per cent in the length of the small intestine, and an increase of only 9.2 per cent in the length of the colon.

The indicated decrease of 7.2 per cent in the length of the small intestine during an age increase from twenty to eighty years, is, when viewed in association with the indicated simultaneous increase of 20.2 per cent in the length of the colon, also worthy of consideration.

Tuberculosis proves to be associated not as has been previously reported, with a decreased length of intestine, but rather with a slight increase of 0.65 per cent in the length of the colon, and an increase of 2.9 per cent in the length of the small intestine.

By contrast, carcinoma and gall stones, the two other diseases considered in relation to intestinal length, both prove to be associated with a length of intestine somewhat shorter than normal.

Table VII.
Growth and Length of the Human Intestine.
Both Sexes.
Relation to Disease

Sex	No. of Obs.	Disease	Small Intestine.									Colon.					
			Length in Metres									Length in Metres.					
M	F		1	2	3	4	5	6	7	8	9	0	1	2	3		
31	7	34									1.00	1.53	13.25			
15	13	28									1.00	1.39	2.25			
6	17	23									1.00	1.51	2.38			
											Average			Max.		
											Min.			Max.		

TABLE IX.—SMALL INTESTINE: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO BODY LENGTH.

Body length in centimeters.	Sex.		Total obs.	Average length in meters.	Percentages.		
	M.	F.			Less than 5 m.	5 m. to 7 m.	More than 7 m.
150 to 155	3	14	17	6.05	11.8	70.6	17.6
155 to 160	8	26	34	5.69	2.9	85.3	11.8
160 to 165	21	17	38	6.14	10.5	63.2	26.3
165 to 170	22	3	25	6.38	4.0	64.0	32.0
170 to 175	22	2	24	6.24	0.0	70.8	29.2
175 to 180	13	0	13	6.51	7.6	45.7	45.7
Summary	89	62	151	6.17	6.0	68.8	25.2

TABLE X.—SMALL INTESTINE: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO AGE PERIODS.

Age (in decades).	Sex.		Total obs.	Average length in meters.	Percentages.			Body length in centimeters.		
	M.	F.			Less than 5 m.	5 m. to 7 m.	More than 7 m.	Av.	Max.	Min.
20 to 29	9	6	15	6.45	0.0	66.7	33.3	165	182	155
30 to 39	21	11	32	6.52	3.1	50.0	46.9	166	182	145
40 to 49	13	13	26	5.99	7.7	76.9	15.4	161	185	149
50 to 59	28	14	42	6.07	9.5	69.1	21.4	162	175	149
60 to 69	18	11	29	5.99	10.3	75.9	13.8	154	177	152
70 to 79	5	11	16	5.98	6.3	75.0	18.7	158	176	140
Summary	94	66	160	6.17	6.9	68.1	25.0	161	185	140

TABLE XI.—SMALL INTESTINE: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO DISEASE.

Disease.	Sex.		Total obs.	Average length in meters.	Percentage.			Body length in centimeters.		
	M.	F.			Less than 5 m.	5 m. to 7 m.	More than 7 m.	Av.	Max.	Min.
Tuberculosis.	31	7	38	6.29	5.3	65.8	28.9	165	182	155
Carcinoma . .	15	13	28	5.86	14.3	71.4	14.3	166	182	145
Gall stones . .	6	17	23	5.73	13.0	74.0	13.0	161	185	149

Sex appears as a definite factor in the question of intestinal length in the adult, for the male small intestine averages about 12 per cent longer than the female small intestine, and the male colon averages about 17 per cent longer than the female colon, for the same body lengths.

TABLE XII.—SMALL INTESTINE: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO SEX.

Sex.	Total obs.	Average length in meters.	Percentages.		
			Less than 5 m.	5 m. to 7 m.	More than 7 m.
Male (160 to 165 cm.) . . .	21	6.53	4.8	61.9	33.3
Female (160 to 165 cm.) . . .	17	5.78	17.7	64.7	17.6
Both (155 to 175 cm.) . . .	121	6.11	4.9	71.1	23.9

TABLE XIII.—COLON: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO BODY LENGTH.

Body length.		Total obs.	Average length in meters.	Percentages.		
Feet and inches.	Centimeters.			Less than 1.25 m.	1.25 m. to 2 m.	More than 2 m.
4'11" to 5'1"	150 to 155	17	1.52	35.3	52.9	11.8
5'1" to 5'3"	155 to 160	34	1.52	11.8	79.4	8.8
5'3" to 5'5"	160 to 165	38	1.40	23.7	57.9	18.4
5'5" to 5'7"	165 to 170	25	1.65	4.0	76.0	20.0
5'7" to 5'9"	170 to 175	24	1.50	8.3	83.4	8.3
5'9" to 5'11"	175 to 180	13	1.66	0.0	69.2	30.8
Summary		151	1.54	14.6	70.2	15.2

TABLE XIV.—COLON: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO AGE.

Age (in decades).	Total obs.	Average length in meters.	Percentages.		
			Less than 1.25 m.	1.25 m. to 2 m.	More than 2 m.
20 to 29	15	1.43	13.3	80.0	6.7
30 to 39	32	1.58	12.5	75.0	12.5
40 to 49	26	1.41	23.1	69.2	7.7
50 to 59	42	1.53	19.0	64.3	16.7
60 to 69	29	1.60	17.2	62.1	20.7
70 to 79	16	1.72	0.0	81.3	18.7
Summary	160	1.55	15.6	70.0	14.4

Table XVIII presents two series of ratios, covering three age periods as follows: body length in relation to the length of the small intestine and of the colon; and the length of the colon in relation to the length of the small intestine. It is believed that the groups of cases upon which these ratios are based, are more carefully arranged

TABLE XV.—COLON: PERCENTAGE VARIATIONS IN LENGTH IN RELATION TO DISEASE.

Disease.	Total obs.	Average length in meters.	Percentages.		
			Less than 1.25 m.	1.25 m. to 2 m.	More than 2 m.
Tuberculosis	38	1.53	18.4	71.1	10.5
Carcinoma	28	1.39	39.3	50.0	10.7
Gall stones	23	1.51	13.0	74.0	13.0

TABLE XVI.—COLON: PERCENTAGE VARIATION IN LENGTH IN RELATION TO SEX.

Sex.	Total obs.	Average length in meters.	Percentages.		
			Less than 1.25 m.	1.25 m. to 2 m.	More than 2 m.
Male (160 to 165 cm.) . . .	21	1.62	19.0	52.4	28.6
Female (160 to 165 cm.) . .	17	1.36	29.4	64.7	5.9
Both (155 to 175 cm.) . . .	121	1.52	13.2	72.7	14.1

TABLE XVII.—GROWTH AND LENGTH OF THE HUMAN INTESTINE.

Percentage Increase or Decrease in Length in Relation to Four Variants: Body Length, Age, Disease, Sex.

Type of variant.	Percentage increases or decreases in length of the intestine.				Percentage increase in body length.
	Small intestine.		Colon.		
	Increase.	Decrease.	Increase.	Decrease.	
1. Body length:					
Fetal (increase in length), 13.4 cm. to 50 cm. . . .	757.0	..	744.0	..	272.0
Birth to adult (increase in length), 50 cm. to 161 cm. . . .	104.0	..	181.0	..	222.0
Fetal to adult (increase in length), 13.4 cm. to 161 cm. . . .	1645.0	..	2900.0	..	1102.0
Adult (increase in length), 150 cm. to 180 cm. . . .	7.6	..	9.2	..	20.0
2. Age:					
Increase from 20 to 80 years	7.2	20.2		
3. Disease:					
Tuberculosis	2.9	..	0.65		
Carcinoma	4.17	..	8.5	
Gall stones	6.20	..	0.65	
4. Sex:					
Male	6.8	..	6.5		
Female	5.4	..	10.5	

NOTE.—In Group 1 the percentage variations are based upon the lengths of intestine determined as normal for the given body lengths. In Groups 2, 3 and 4 the percentage variations are based upon the following lengths determined as normal or the adult. Small intestine, 6.11 m.; and colon, 1.52 m.

TABLE XVIII.—GROWTH AND LENGTH OF THE HUMAN INTESTINE.

Ratios of Body Length to Small Intestine and Colon, and Colon to Small Intestine at Three Age Periods: the Early Fetus, Birth, and the Adult, in Both Sexes.

Total obs.	Sex.		Age periods.	Body lengths in cm.			Ratios.		
	M.	F.		Min.	Av.	Max.	B. L.: S. I.	B. L.: C.	C.: S. I.
5	1	4	Fetus (3 to 4 mos.)	12.5	13.4	15.5	1:2.6	1:0.5	1:5.4
10	3	7	Birth	48.0	50.0	52.0	1:6.0	1:1.1	1:5.5
21	21	0	Adult (27 to 72 years)	160.0	162.0	165.0	1:4.0	1:1.0	1:4.0
17	0	17	Adult (20 to 69 years)	160.0	162.0	165.0	1:3.6	1:0.8	1:4.2
121	73	48	Adult (20 to 80 years)	155.0	161.0	175.0	1:3.7	1:0.9	1:4.0

B. L. = body length; S. I. = small intestine; C. = colon.

with regard to uniformity than those heretofore available in the literature. From this Table it will be seen that the small intestine is longest in relation to body length at birth. In the adult, the ratio of body length to small intestinal length is about 1:3.7, the ratio of colon length to small intestinal length being about 1:4.0. In a word, it may be said that in the adult, colon length about equals body length, the small intestine being about four times the length of the body.

One additional point may be mentioned; this is in reference to the assertion by Treves concerning the development of the sigmoid loop at and immediately after birth. In 19 males and 15 females of my series, a total of 34 fetal cases, observations upon the length and appearance of the sigmoid loop were recorded, with the following results. Of the 19 males, 12 had long and 7 had short sigmoid loops. Of the 15 females, 8 had long and 7 had short sigmoid loops. There was thus a total of 34 fetal cases in which 20 had long and 14 had short or normal sigmoid loops, yielding 58.8 per cent with long, and 41.2 per cent with short or normal sigmoid loops. About one-third of a smaller number of cases, all of exactly 50 cm. in length, were found to have sigmoid loops not excessive in length. It would seem that these findings are adequate to prove incorrect, Treves' sweeping statements concerning the development of the sigmoid loop at and immediately after birth.

Summary. Recent literature upon the growth and length of the human intestine, is conspicuous by its absence.

The older literature is often contradictory, possibly because it was based upon inadequate sources.

There is presented in this paper what is believed to be a larger and perhaps a more accurate series of data with regard to intestinal growth and length, than has heretofore been available for reference. Certain results of this study would seem to warrant special consideration. Among them, the following may be mentioned.

1. There is a total variation of about 100 per cent in the length of the small intestine and the colon. This variation begins not at or after birth, as has been stated by previous investigators, but at or before the fifth month of fetal life.

2. Evidence is presented to show that Treves is incorrect in stating that all children start life with "practically the same length of intestine." Furthermore, the evidence available does not support his statement that "there is no growth in length of the colon during the first four months after birth." Also, the sigmoid loop certainly is not always of excessive length at birth; therefore, Treves cannot be correct in stating that the uniformly long sigmoid loop goes through identical evolutions in all infants during the first four months after birth.

3. Without exception, all male and female children examined, of a body length greater than 60 cm., had already acquired a small intestine longer than the minimum length compatible with prolonged adult life. But at this same early period of life, these children had not yet acquired much over half the corresponding length of colon.

4. Not later than the tenth year of age, practically all the children examined had already acquired both small intestines and colons of lengths such that had they been found in the adult, they would have been classified as within the normal adult limits of intestinal length.

It would appear then, that from the tenth year of age onward, intestinal growth is an affair primarily not of increase in actual length, but of increase in area through increase in caliber.

5. Although in all groups of cases examined, there existed a total variation in intestinal length of 100 per cent or more, it may be noted that almost three-quarters of all the adult cases examined had small intestines and colons varying in length not more than about 17 per cent above or below the calculated average lengths of intestine and colon.

Thus, about 70 per cent of all the adults examined had a small intestine varying in length between 5 and 7 meters, with an average length of 6.11 meters. Under the same circumstances, the colon varied in length from 1.25 to 2.00 meters, with an average length of 1.52 meters.

At least from a surgical point of view, it is of interest to note the minimum length of intestine compatible with adult life, as determined by the measurements in my series of 242 cases. The minimal

small intestinal length recorded was 3 meters, the maximal being 8.5 meters. For the colon, the minimal length recorded was 1 meter, the maximal length being 3.25 meters. These measurements do not include the length of the duodenum and rectum.

6. With one exception, variations in intestinal length possibly associated with body length, age, disease, and sex, do not exceed 10 per cent.

This exception is an increase of 20 per cent in the length of the colon with an age increase from twenty to eighty years. The cause of this increase is not determined. It is however, associated (during this same age increase from twenty to eighty years), with a decrease of 7 per cent in the length of the small intestine. Perhaps in addition to a certain amount of stretching of the colon which one might expect as a result of many years of abuse, there may actually be going on from birth to old age a progressive change in the character of the intestinal canal sufficient to bring the senile individual into definite contrast with the newborn baby from a dietary point of view; *i. e.*, the senile individual may have become structurally less well adapted to live upon a high protein diet than the baby for whose welfare such a diet is essential.

7. It has been frequently asserted that the tuberculous individual is at a disadvantage on account of his having an intestine actually shorter than normal in length. These assertions are not supported by the results of my measurements in a group of 38 cases dying of this disease, for these indicate that the tuberculous individual is in fact possessed of an intestine and colon of normal length.

By contrast, the existence of an intestinal length shorter than normal both as to small intestine and colon, was demonstrated in a group of 28 cases dying of carcinoma. Also, a small intestine slightly short in length but associated with a colon normal in length, was demonstrated in a group of 23 gall stone cases.

Conclusions. 1. The most striking characteristic of the human intestine is extreme variation in length. This variation averages about 100 per cent.

2. This variation in length begins at or before the fifth month of age in the fetus, and thereafter is in evidence throughout life, in both small intestine and colon, in both sexes.

3. In the fetus at full term, the length of the intestine is not "singularly constant," nor do all children start life, according to Treves, with "practically the same length of intestine." On the contrary, the characteristic 100 per cent variation in length of the intestine is in evidence at birth as at all later periods of life.

4. The colon does not, as Treves stated, invariably cease growth "for at least the first four months of extrauterine life."

5. The sigmoid loop cannot, as Treves stated, always go through the same evolutions immediately after birth, because at birth the sigmoid loop is by no means always of excessive length; on the

contrary, the sigmoid loop is at birth not infrequently shorter in length than would be considered normal.

6. The small intestine is shortest in relation to body length in the fetus of three to four months of age. It is longest in relation to body length at birth, and it again becomes shorter in relation to body length during adult life.

The length of the colon in relation to the length of small intestine, remains about the same from early fetal life to birth. After birth, the colon continues throughout life to increase slowly in length, actually and in relation to the length of the small intestine. The small intestine on the contrary actually decreases in length with advancing age.

7. From the point of view of comparative anatomy, the newborn child approaches the carnivorous in type, as evidenced by its ratio of length of small intestine to colon. By contrast, the senile adult, with his decreased length of small intestine and increased length of colon, is becoming less and less well adapted to live upon the high protein diet so necessary for the maintenance of health in the normal infant.

8. The child of 60 cm. in length (6 months or less in age) has already acquired about one-half the minimal adult length of colon.

9. The child of 60 cm. in length (six months or less in age) has already acquired a small intestine longer than the minimum compatible with adult life.

10. The child of ten years of age has both a small intestine and a colon of a length considered normal for the adult.

11. Growth of the intestine after ten years of age, proves to be an affair primarily not of growth in length, but of growth in caliber.

12. About 70 per cent of all adults have a small intestine varying not over 35 per cent in length (5 to 7 meters), with an average length of about 6 meters.

13. About 70 per cent of all adults have a colon varying in length not over 42 per cent (1.25 to 2.00 meters) with an average length of about 1.50 meters.

14. The colon of the adult increases about 20 per cent in length, with an increase in age from twenty to eighty years. With this exception, variations in the length of the intestine possibly associated with body length, age, and disease, do not exceed those due to sex alone. Variations in length due to sex alone do not exceed 10 per cent.

15. In the adult, the male has a small intestine and colon about 6 per cent longer than the general adult average. In the female, the small intestine is about 5 per cent, and the colon about 10 per cent shorter than the general adult average.

16. The normal average length of the small intestine in the adult, may be considered as 6.11 meters, or 20 feet 6 inches. The normal average length of the colon in the adult, may be considered as 1.52 meters, or 5 feet 2 inches:

REFERENCES.

1. Bardeen: *Am. Jour. Anat.*, 1914, 16, 427.
2. Bean: *Bull. Johns Hopkins Hosp.*, 1912, 23, 363.
3. Beneke: *Deutsch. med. Wehnschr.*, 1880, 6, 433, 448.
4. Bryant: *Boston Med. and Surg. Jour.*, 1915, 172, 321; 1915, 173, 384; 1916, 174, 412.
5. Crampe: *Arch. f. Anat., Physiol. u. wissenschaft. Med.*, 1872, p. 659.
6. Custor: *Arch. f. Anat., Physiol. u. wissenschaft. Med.*, 1873, p. 478. Ueber die relative Grosse des Darmkanals und der Hauptsachlichsten Körpersysteme beim Menschen und bei Wirbelthieren, Bern, 1873.
7. Cuvier: *Lecons d'anatomie comparee*, Paris, 2d ed., 1835, 4, 172.
8. Deakin: *Proc. Northwest Provinces and Oudh Branch Brit. Med. Assn.*, Allahabad, 1883, 2, 90.
9. Dreike: *Deutsch. Ztschr. f. Chir.*, 1895, 40, 43.
10. Editorial, *Brit. Med. Jour.*, 1885, 1, 495.
11. Frolosky: *Beitr. z. Anat. des Verdauungskanals der Sauglinge*, Diss., 1880.
12. Henle: *Handb. d. systemat. Anat.*, 1862, 2, 83.
13. Henning: *Centralbl. f. med. Wissensch.*, 1881, 19, 433.
14. Huschke: *Baue des Mensch. Korp.*, 1884, 5, 109.
15. Kretschmann: *Grosse des Herzens und Darmes bei Phthisikern.*, Diss. Petersburg, 1890.
16. Lamb: *AM. JOUR. MED. SCI.*, 1893, 105, 639.
17. Meckel: *System der vergleichenden Anatomie*, 1821, 4; *Deutsch. Arch. f. d. Physiol.*, 1817, 3, 160.
18. Robinson: *Mathew's Med. Quart.*, Louisville, 1895, 2, 338.
19. Rolssenn: *Ein Beitrage zur Kenntnis der Langenmaasse des deutschen Darms.*, Dorpater Diss., 1890, p. 53.
20. Spigelius: *De Humani Corporis Fabrica*, Frankefurti, 1632, 8, 293.
21. Swaim: *Boston Med. and Surg. Jour.*, 1912, 167, 249.
22. Tarenetsky: *Mem. Acad. imp. d. sc. de St. Petersburg*, 1881, 28.
23. Treves: *Brit. Med. Jour.*, 1885, 1, 415.
24. Werner: *Biolog. Centralbl.*, 1884, 14, 117.

THE VARIATIONS IN GASTRIC SECRETION OF THE NORMAL INDIVIDUAL.

By J. R. BELL, M.D. (MELB.), M.R.C.P. (LOND.),

AND

WM. MACADAM, M.A., M.D. (GLASG.), M.R.C.P. (LOND.),

MEDICAL TUTOR AND REGISTRAR, UNIVERSITY OF LEEDS.

Introduction. The fractional method of gastric analysis, by revealing the great variations in gastric acidity which may occur both in health and disease, has thereby been subjected to unfair criticism. It is unjustifiable to apportion the whole blame to a method when we are yet unable to interpret fully and accurately the results obtained. Even in its present form, and with our meagre knowledge of the probable normal standards and possible variations, the fractional method supplies more information than the single one-hour test, and must inevitably replace the latter if gastric analysis is to be accorded a place in diagnostic medicine.

Modification in the technic in the light of certain defects, however, seems desirable.

In order that the results obtained in pathological conditions may be assessed at their true value, it is essential that we should know what variations in secretion and motility may occur in the normal individual when subjected to this method of investigation. With this object in view, Rehfuß, Bergeim, Hawk, Fowler, Zentmire,^{1 2 3} Bennett and Ryle⁴ and others examined series of normal individuals of both sexes, but, so far as we are aware, there is no published record of a series of fractional test-meals carried out over a prolonged period in the same individual under constant conditions. Kopeloff⁵ investigated normal individuals at intervals of several days, but does not state how many tests were done. He concluded that repeated analyses on the same individual within a short period of time yielded different acid curves. Lyon, Bartle and Ellison,⁶ in remarking on the variations in the acid values in different normal persons say, "If the stomach contents of the same individual are examined daily under the same conditions of time and length of preceding fast, great variations of acid values will frequently be seen." Bennett and Ryle,⁴ on the other hand, affirm that "in several instances exactly identical curves have been obtained when taken on different occasions; in general, it has been found that slight differences may be found toward the end of the curve, corresponding with the amount of duodenal regurgitation at a particular moment."

We therefore considered it desirable to study the variations in gastric response to the same test-meal repeated under the same conditions on twenty consecutive days (Sundays excepted) in a healthy subject. At the same time the opportunity was taken of comparing these findings with those obtained with several other types of test-meal in general use.

Method of Procedure. The investigations were carried out on a healthy man, aged thirty-one years; weight, 10 stone 4 pounds; height, 5 feet 6 inches; of good physique; had had no previous illnesses and gave no history of any gastro-intestinal disturbance whatever. After a preliminary examination of several individuals we purposely selected this subject, as his stomach showed a good secretory response to the meal, and he displayed an intelligent interest in our experiments and underwent the examination without any apprehension or discomfort. As far as possible he observed the same daily routine with regard to meals and habits throughout the whole period of investigation. He took no food or drink after 10 P.M., and each morning at 9.30 he swallowed a Ryle (modified Einhorn) tube. The fasting contents of the stomach were completely withdrawn and the standard test-meal of 1 pint of oatmeal gruel, as employed by most workers on fractional gastric analysis, was given. Subsequently, 10 cc specimens

were aspirated at intervals of a quarter of an hour for two and three-quarter hours. As not infrequently occurs, there was moderate salivation during the test. Measures were taken to prevent swallowing of this saliva, the amount collected during the two and three-quarter hours averaging 250 to 300 cc.

Discussion of Results. Reproductions of the charts which were drawn up illustrate the points of similarity between the curves and such daily variations as were present, more clearly than a composite chart or verbal description.

The first impression obtained from a study of the charts is that they are markedly dissimilar. On closer examination this is shown to be dependent on daily fluctuations in the acid values of the different "fractions," and that, with the exception of the curves of the first and possibly of the third bag, the remainder exhibit many points of similarity and are of the same type.

From the practical standpoint, the fact that the lowest curve of the series was that obtained on the first examination raises an important question. In the ordinary course this is the curve that would have been taken as representing the secretory activity of this individual's stomach, and would have been classed as a "normal," according to the scheme adopted by one of us.⁷ As to the factor or factors responsible for this low secretion as compared with the subsequent examinations, we are inclined to the view that it is a psychological inhibition due to the natural apprehension so commonly noted on the first occasion of swallowing the tube. Bennett and Venables⁸ have demonstrated this effect of the emotions on gastric secretion. In our opinion nausea did not play much part in the secretory inhibition in this case; nor did the reputed neutralization of the acid by swallowed saliva take place, as this was carefully avoided throughout the whole series of examinations.

This observation points to a possible fallacy in the investigation of pathological conditions and suggests that if on the first examination a hypochlorhydric or normal curve is obtained, and even more so if the clinical evidence suggests a higher curve of acidity, the test should undoubtedly be repeated before eliminating the possibility of a higher acid secretion.

It may here be mentioned that on two occasions on which the alkalinity of the saliva was estimated it was found to require for neutralization $30 \text{ cc } \frac{N}{10} \text{ HCl}$ per 100 cc while the total amount secreted averaged 300 cc. Such an amount of alkali distributed over the two and three-quarter hours will lower the acid curves slightly. We accordingly carried out two tests while the patient swallowed all saliva. No appreciable difference was to be observed in these curves as compared with those of the series already discussed. It is obvious, however, that such a factor might play a part in leading to a low acidity in a subject who was not of the "hyperchlorhydric" type.

TYPE OF ACID CURVE. It is not to be expected that an individual's curve of gastric acidity during a test-meal will exhibit exactly the same characteristics and details on every occasion, for many factors, both known and unknown, may cause slight deviations. However, in such a subject as we have examined, and under conditions as nearly constant as possible, we should anticipate, *a priori*, that the acid curves on the various occasions would show some constant characteristic feature, although possibly differing in detail. Such is seen to be the case for, almost without exception, the meal provokes an immediate abundant secretion of acid, the curve of acidity loses very little time in rising to a considerable height and this is more or less maintained until digestion has been completed. Thereafter it quickly falls to a level approximating to that of the fasting contents, to be followed by a slight rise which is maintained to the end of the test. This common characteristic of the various curves is most striking, notwithstanding the wide variations in the degree of acidity attained. Thus if we exclude the first and the third, all the curves would be classified either as mild or definite hyperchlorhydria.

Another noteworthy point is that the curves of free HCl and total acidity bear the same relation to each other throughout the series. Experience in fractional gastric analysis soon teaches the observer the folly of laying stress upon slight deviations in the curves, and leads him to rely more and more for his deductions on the type of curve taken as a whole. Ryffel⁹ and others have already emphasized this point, and the present findings afford additional evidence of the necessity for observing this precaution.

FASTING CONTENTS OF THE STOMACH. The amounts obtained varied between 3 cc and 38 cc, with an average of 17.8 cc. This variation is in accordance with Ryle's¹⁰ experiments on himself, in which over a period of thirty days the amount varied from "1 or 2 cc obtained with difficulty to 15 or 30 cc obtained with ease." The free HCl values varied between 0 and 22, averaging 8.5, and the total acidity values between 8 and 40, averaging 23.4. Ryle's corresponding figures were 0 to 22 and 4 to 38. These variations are to be expected, for duodenal reflux, swallowed saliva, and presence or absence of hunger sensations must necessarily vary from day to day. On only one occasion was bile visible in the fasting contents and then only in very small amount.

RATE OF EMPTYING OF THE STOMACH. This was a remarkably constant feature. The average time of emptying was one and three-fifths hours, with a range from one and a half to two hours. This finding was confirmed by roentgen-ray examination, for the report of which we are indebted to Dr. Leo A. Rowden, of Leeds. He says: "This individual's stomach is normal in every respect. It is orthotonic in type, and peristalsis is of normal activity. After a meal of 1 pint of oatmeal gruel containing 2 ounces of bismuth carbonate the stomach was empty in one and three-quarter hours."

TABLE I.

Specimen.	Free HCl.			Total acidity.		
	Average.	Standard deviation.	Coefficient of variation (per cent).	Average.	Standard deviation.	Coefficient of variation (per cent).
Fasting juice	8.50	8.115	95.5	23.45	9.764	41.6
$\frac{1}{4}$ hr. . .	3.80	7.586	199.6	23.75	10.449	44.0
$\frac{1}{2}$ hr. . .	24.80	16.497	66.5	51.45	18.159	35.3
$\frac{3}{4}$ hr. . .	47.50	18.800	39.6	70.15	17.431	24.8
1 hr. . .	56.35	14.523	25.8	74.10	13.924	18.8
$1\frac{1}{4}$ hr. . .	48.26	17.474	36.2	62.63	17.824	28.5
$1\frac{1}{2}$ hr. . .	41.60	20.375	49.0	55.35	20.558	37.1
$1\frac{3}{4}$ hr. . .	33.65	19.239	57.2	46.85	19.691	42.0
2 hr. . .	27.26	15.617	57.3	40.47	16.359	40.4
$2\frac{1}{4}$ hr. . .	26.40	15.406	58.4	40.10	14.798	36.9
$2\frac{1}{2}$ hr. . .	29.15	12.130	41.6	42.00	13.472	32.1
$2\frac{3}{4}$ hr. . .	31.00	14.287	46.1	44.11	14.843	33.7

The average values of free HCl and total acidity calculated in terms of cubic centimeters of N/10 NaOH required to neutralize 100 cc of gastric juice together with the standard deviations and coefficients of variation of the various specimens.

As may be gathered from our previous remarks, although the results of gastric analysis are conveniently recorded by the graph method, we do not consider that statistical methods can be reasonably applied to the elucidation of such curves. A false impression of mathematical exactitude is thereby suggested which is wholly misleading when applied to a phenomenon which physiologically varies within such wide limits.

We have, however, submitted our figures to Dr. Matthew Young, of the Medical Research Council Statistical Department, and are greatly indebted to him for working out the standard deviation, that is, the degree of scatter or variation in the distribution of the different acid values. This is recorded in Table I along with the coefficient of variation which enables us to compare the several distributions as regards the degree of variation present. One interesting fact emerges from this study, viz., the coefficient of variation for both free HCl and total acidity is lowest in the one-hour specimens. That is to say, if reliance has to be placed upon the examination of a single specimen, then that withdrawn at the end of one hour appears to give the most constant values for the degree of acidity. From the statistician's standpoint, however, it must be noted that the coefficient of variation in this fraction is still very considerable, viz., 25.8 per cent and 18.8 per cent for the free HCl and total acidity respectively.

COMPARISON BETWEEN VARIOUS TEST-MEALS. Rehfuss and Hawk¹¹ and Knapp¹² have urged the universal adoption of a standard test-meal. Unfortunately at the present time so desirable a

condition does not obtain; therefore, on completing the series of twenty consecutive examinations with the oatmeal gruel test-meal, we investigated certain of the other meals commonly employed, with the following results.

1. *Two slices (60 gm.) of bread without crust and 500 cc water:* The curves conformed in every way to those obtained in the above series, and the stomach emptied at the same rate. If, therefore, the oatmeal-gruel meal is not available the bread-and-water meal will give the same information, and data obtained with this meal may fairly be compared with those obtained with the oatmeal gruel. Nevertheless, we would not advise bread and water as the routine meal, for unless the tube is re-swallowed after the fasting contents of the stomach are withdrawn, efficient mastication is somewhat difficult and the small holes in the tube are more liable to become blocked.

2. *Two slices (60 gm.) of toast without crust and 400 cc tea with milk and sugar:* The curves approximated to the higher ones obtained in the above series and exhibited exactly the same characters. The rate of emptying of the stomach was unaltered. No difficulty was experienced in withdrawing the specimens, nor in their titration, but owing to the brownish color the end-point was not so distinct. Moreover, bile and blood in small amounts could be easily overlooked.

3. *Arrowroot biscuits, 60 gm., and 500 cc water.* The curves obtained resembled the lower ones in the above series and manifested the same general characters. There was, however, a greater divergence between the curves of free HCl and total acidity in the earlier stages of digestion. This is probably due to the more finely divided particles being able to "mop up" more readily the acid secreted. The specimens withdrawn were extremely homogeneous. The rate of emptying of the stomach was unaltered.

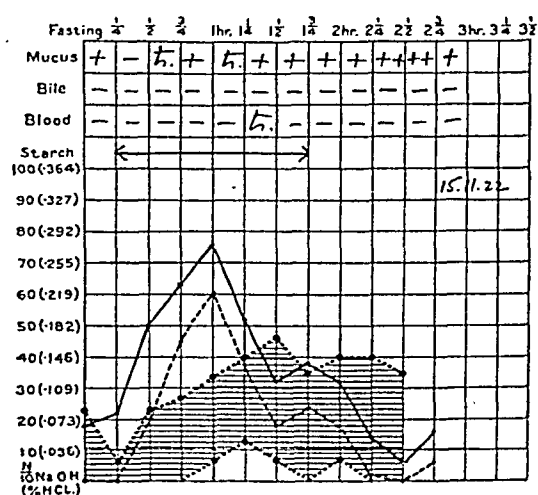
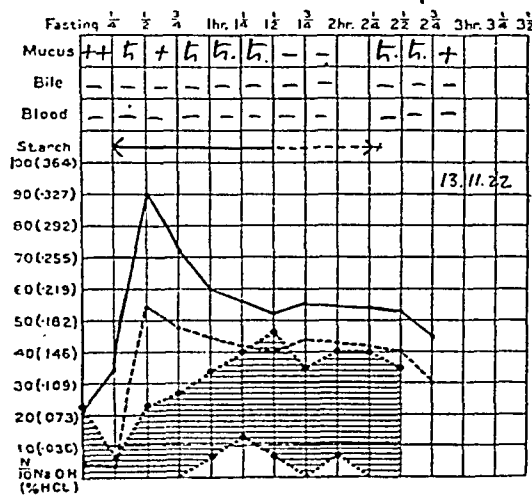
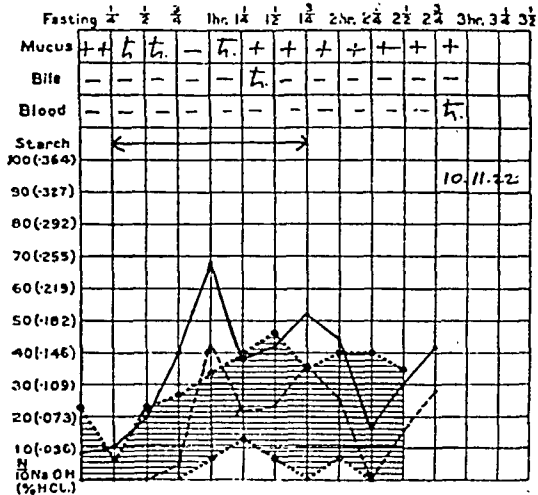
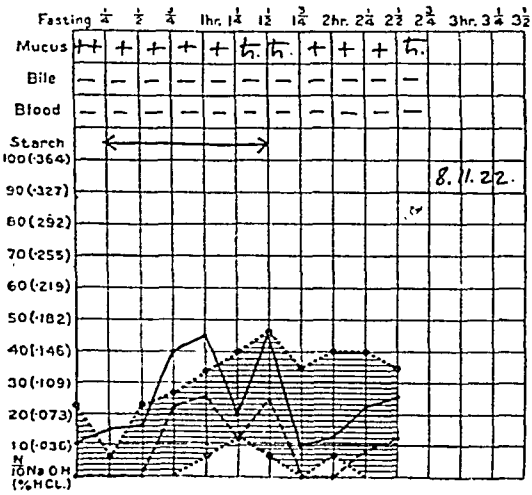
4. *Peptone, 5 gm., and sodium salicylate, 0.1 gm., in 250 cc water:* (As recommended by Delort and Verpy.¹³) A rapid rise in the free HCl curve resulted so that the highest value was reached in three-quarters of an hour. The descent in the curve was equally rapid, no free HCl being found at the end of one and a half hours. No trace of sodium salicylate was to be found at the end of half an hour (the evidence accepted by Delort of complete evacuation of the stomach). This meal appears to us to be quite unsuitable for routine use.

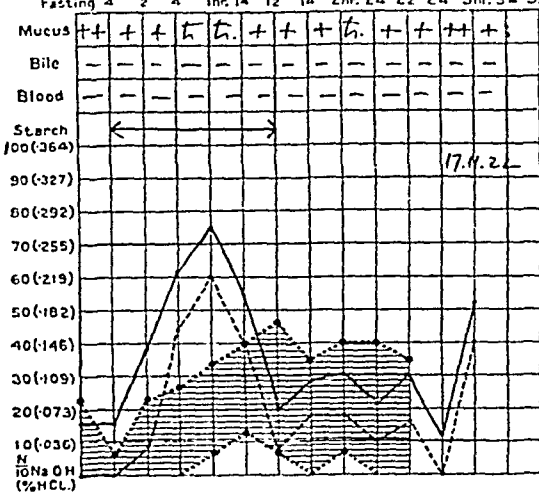
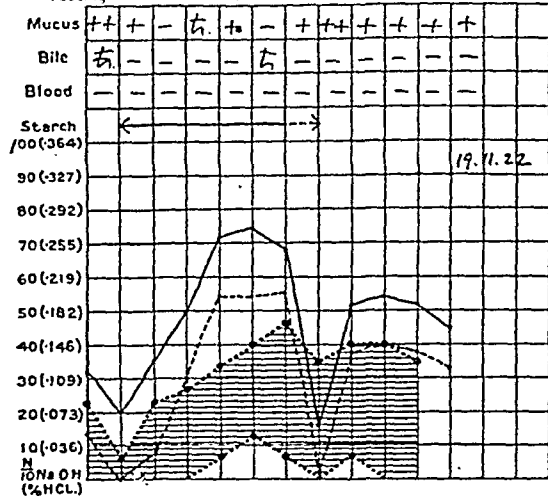
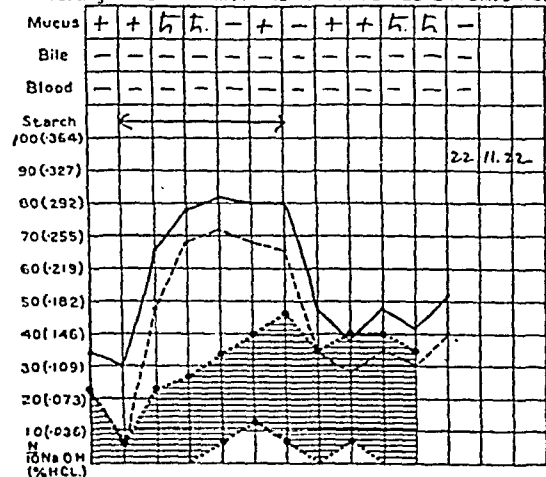
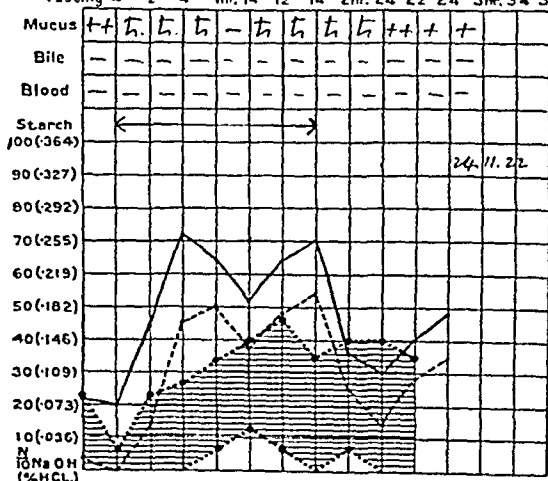
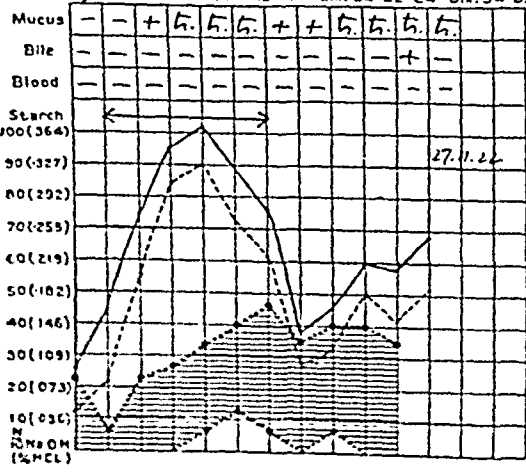
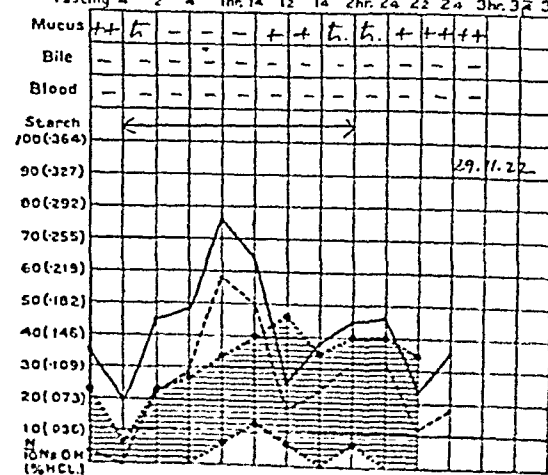
5. *Standard oatmeal gruel, 2 pints:* The curve obtained with this "double" meal made a more gradual ascent than those in the above series, and did not reach its fastigium (which was 60 units for the free HCl) until one and three-quarter hours had elapsed. The descent was also more gradual and altogether the curve did not resemble at all closely those hitherto obtained. The rate of emptying of the stomach was only slightly, if at all, delayed.

CHARTS FOR THE ALTERNATE DAYS OF FRACTIONAL GASTRIC INVESTIGATION CARRIED OUT ON THE SAME INDIVIDUAL ON TWENTY CONSECUTIVE DAYS.

The shaded area represents the limits for free HCl (dimethyl indicator) of 80 per cent of normal people (Bennett and Ryle).

..... represents free "HCl" } calculated in terms of ccs of $\frac{N}{10}$ NaOH.
————— represents total acidity }



Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$

 Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$

 Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$

 Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$

 Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$

 Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr. $3\frac{1}{4}$ $3\frac{1}{2}$


Summary. 1. A study has been made, by means of the fractional method, of the gastric response of a healthy individual to the same test-meal, under the same conditions, on twenty consecutive days.

2. The lowest acid curve of the series was obtained at the first examination. Subsequently, with one exception, the curves of free HCl and total acidity were of a characteristic type and the degree of acidity varied between a mild and a definite hyperchlorhydria. They serve to show, however, the range of variation which may occur in the same individual in a series of examinations.

3. The rate of emptying of the stomach was remarkably constant throughout the whole investigation, and was confirmed by roentgen-ray examination.

4. The "standard deviation" and the "coefficient of variation" of the acidities of the different specimens at corresponding times were determined. The coefficient of variation for both free HCl and total acidity was lowest in the one-hour specimens. That is, the acid values of this fraction varied within the narrowest range.

5. Several of the other test-meals in common use were employed and the results obtained compared with the "oatmeal-gruel" series. The "tea and toast" meal provoked a slightly greater acid secretion than the average one obtained with oatmeal gruel.

6. One practical point emerges, viz., if a low or normal acid curve is obtained on the first examination, when the clinical history of the patient suggests a hyperchlorhydria, the test should be repeated before a high degree of acidity can be eliminated.

In conclusion we wish to express our thanks to Prof. M. J. Stewart for affording us facilities for carrying out this investigation in the pathological department of the University of Leeds.

BIBLIOGRAPHY.

1. Rehfuess, Bergeim and Hawk: Jour. Am. Med. Assn., 1914, 63, 909.
2. Fowler, Rehfuess and Hawk: Jour. Am. Med. Assn., 1915, 65, 1021.
3. Fowler and Zentmire: Jour. Am. Med. Assn., 1917, 68, 167.
4. Bennett and Ryle: Guy's Hosp. Rep., 1921, 71, 286.
5. Kopeloff: Jour. Am. Med. Assn., 1922, 78, 404.
6. Lyon, Bartle and Ellison: New York Med. Jour., 1921, 114, 272.
7. Bell: Guy's Hosp. Rep., 1922, 72, 302.
8. Bennett and Venables: Brit. Med. Jour., 1920, 2, 662.
9. Ryffel: Lancet, 1921, 1, 586.
10. Ryle: Guy's Hosp. Rep., 1921, 71, 163.
11. Rehfuess and Hawk: Jour. Am. Med. Assn., 1921, 76, 371.
12. Knapp: New York Med. Jour., 1922, 115, 695.
13. Delort and Verpy: Compt. méd. d. séances de la Soc. de biol., 1920, 83, 1470.

THE EFFECTS OF ROENTGEN-RAY ENERGY ON THE SPLEEN.

BY CHARLES H. HARBINSON,

DEPARTMENT OF ANATOMY, UNION UNIVERSITY (ALBANY) MEDICAL COLLEGE,
ALBANY, N. Y.

THIS paper deals with the changes that take place in the normal rabbit following roentgen radiation of the spleen. The experiments tabulated (see Table) give the data to show the food intake, urine output, changes in weight, red, white and differential counts following exposure of the normal spleen to the roentgen-ray. The writer became interested in this subject following the work of Hall and Whipple¹ on "Roentgen-ray Intoxication" and of Martin and Dennis² on "The Intestinal Reaction to Erythema Dose."

Considerable is known of the ordinary roentgen-ray heat burn, and the evidence is pretty conclusive that body protein in the burned area is so altered that toxic split-products are formed and absorbed into the body. If the toxic protein split-products are in sufficient amount there will result a fatal systemic-intoxication. A general systemic or constitutional reaction follows the use of the large doses of roentgen-rays. This has been the cause of considerable interest on account of the semblance to intoxication in dogs caused by proteose injection. The reaction consists of a loss of appetite, malaise, nausea and vomiting. Several theories have been advanced in an attempt to account for the general systemic effects produced. Hall and Whipple believe the theory of Edsall and Pemberton³ to be the most nearly correct. They state as their belief that tissue destruction accomplished by roentgen-rays undoubtedly involves chiefly tissues rich in nucleoprotein, such as the spleen and liver. The decomposition products of this form of protein are especially rich in substances that are more or less toxic and difficult to metabolize and excrete. Edsall and Pemberton furthermore state that the intoxication is not dependent directly upon alterations in the excreting power of the kidney. Some investigators, Warthin⁴ and Rosenstein⁵ and others, however, charge the constitutional effects following the prolonged exposure of roentgen-rays to the production of a nephritis. Heineke,⁶ the first to make careful histological examination of animals following roentgen-ray exposure, demonstrated that the lymphoid tissues of the body are primarily affected by the roentgen-ray.

In view of the fact that the spleen is a lymphogenic organ rich in nucleoprotein, it would seem interesting to note whether or not a constitutional reaction would follow the exposure of the spleen to a lethal dose of roentgen-ray; whether or not we would, by direct radiation of the spleen, obtain that train of symptoms—

nausea, vomiting, loss of weight, loss of appetite, etc.—which follows the application of large doses of roentgen-ray to the unprotected abdomen or to the exposed loop of small intestine; whether a toxin would be formed through the decomposition of nucleoprotein in the spleen sufficiently toxic to produce a necrosis of the epithelial lining of the ileum, protected from the direct action of the rays.

Method. Normal rabbits, all of the same breed, were used in the experiments. Some preliminary work was necessary to determine the roentgen-ray dose sufficient to produce a constitutional reaction and death within fifteen days. With a 5-inch spark gap, a tube-target distance of $11\frac{1}{2}$ inches, 50 ma. was applied to the lower abdomen of a series of rabbits for periods of time varying from one to fifteen minutes. The voltmeter read 50 kv. It was found in the case of 4 rabbits that 50 ma. applied for fifteen minutes at the above distance invariably produced severe constitutional symptoms on the eighth day following exposure and that these symptoms reached the height of their severity just before death on the eleventh day. In all cases the hair covering the exposed area was shaved off before radiation. A second series of 3 rabbits, to which the same exposure was given over the left hypochondrium, also died on the eleventh day. Records were kept of the red, white and differential counts, food intake, urine output, weight and general condition of a third series of 9 rabbits. All blood counts were made between 9.00 and 11.00 A.M.; the rabbits were kept in individual cages with sharply pitched floors to facilitate the complete collection of urine; after the bleedings the rabbits were fed a quantity of food sufficient to keep their weight constant. If any food remained in the cage at the end of the day—rarely the case—the surplus was removed.

These observations were made over a period of eight days previous to operation and for eleven days thereafter. The rabbits were starved for a day previous to operation. The hair over the left hypochondrium was cut and shaved off, the field scrubbed with green soap and water and then washed with 70 per cent alcohol; under ether, an incision $\frac{3}{4}$ inch long was made over the splenic area; the incision was sufficiently large to permit the pulling out of the spleen through a slit in a sterile towel thrown over the operative field, on to the abdominal wall. A sheet of lead $\frac{1}{4}$ inch in thickness with a hole at the center, the size of which could be regulated to conform to the thickness of the spleen, was then "wrapped" in about the exposed organ, not tightly enough, however, to exert any pressure on it. A slit in the sheet of lead extending from the centrally situated hole to the periphery of the lead shield made it possible to so bend the plate as to reduce the size of the hole. In each case the lead was first scrubbed with hot water and soap and then washed with 70 per cent alcohol. The exposed spleen was

then covered with a 1 to 5000 bichloride pack. The spleens of 2 animals received five- and ten-minute exposures respectively; 4 others received fifteen-minute exposures; the remaining 3 were put through the same routine but were not rayed. The rays came through a window on the left of a lead box surrounding the Coolidge tube. The width of the window was much less than that of the shield shown in the plate so that all other parts of the rabbit were protected save the spleen; it was impossible for any of the rays to enter the abdomen through the slit in the shield because the edges were made to overlap. By deeply anesthetizing the animals just before exposure, it was possible to subject the spleen to the ray for fifteen minutes without interruption. By the time the radiation was completed it was necessary to administer more ether before attempting to sew up the small incision. The spleen was replaced in the abdomen and the incision closed with No. 00 interrupted plain catgut sutures. All layers of the abdomen were included in each suture. The incisions were covered with sterile dressings, and the rabbits returned to their cages. Twenty-five minutes after the completion of the operation the rabbits were on their feet taking food. Observations were made for eleven days following exposure of the spleen, at the end of which time the animals were sacrificed by injecting air into the marginal ear vein. Autopsies were then performed; tissues were placed in Zenker's fluid, imbedded by the paraffin method, and sections stained with hematoxylin and eosin.

TABLE I.

(SR 1, white, spleen rayed ten minutes.)

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 18	...	1.54	10,800	5,280,000	400, carrots	440	Op. 9-10.
	"Op."	Postop.	250	
19	1	1.40	12,800	4,704,000	300, turnips	300	Active.
20	2	...	8,000	...	400, carrots	200	Active.
21	3	1.50	7,800	4,832,000	400, cabbage	300	Active.
22	4	400, carrots	315	Normal.
23	5	1.54	8,400	4,480,000	600, cabbage	400	Normal.
24	6	...	9,800	...	200, turnips	200	Normal.
25	7	1.45	7,400	4,736,000	320, turnips	250	Normal.
26	8	400, turnips	480	Normal.
27	9	1.53	8,600	4,224,000	400, carrots	..	Normal.
28	10	400, cabbage	500	Normal.
29	11	1.54	8,000	...			

DIFFERENTIAL COUNT.

	Polymorpho-nuclears.	Lympho-cytes.	Baso-philus.	Eosino-philus.
Before exposure	43	39	10	2
Five days after	30	58	2	10
Ten days after	48	50	..	2

Experimental Observations. Animal well and active; sacrificed with air embolus injected in ear vein at 9.00 A.M., April 29. Wound healing nicely; spleen of normal size; tip shows pin-head size whitish areas of necrosis. Liver enlarged and of pale color. Entire gastro-intestinal tract apparently normal; no evidence of hemorrhage into the mucosa of the ileum, of desquamation of the villi, etc. Kidneys appear normal. Thorax negative.

TABLE II.
(SR 2, gray, spleen rayed five minutes.)

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 17	...	1.84	9,000	4,832,000	400, carrots	400	Operated on at 11 A.M.; spleen rayed.
	Postop. 300, turnips	..	
18	1	400, carrots	200	Slight infection.
19	2	1.59	19,000	4,608,000	400, carrots	260	
20	3	...	25,600	...	400, cabbage	340	Slight infection; wound washed with H ₂ O ₂
21	4	1.65	14,800	356	
22	5	320	
23	6	1.66	17,000	4,480,000	600, cabbage	310	
24	7	...	17,400	...	400, turnips	345	
25	8	1.71	19,200	4,544,000	400, turnips	300	
26	9	400, turnips	275	
27	10	1.76	10,000	4,736,000	400, carrots		
28	11	1.78	14,000				

DIFFERENTIAL COUNT.

	Polymorpho-nuclears.	Lympho-cytes.	Baso-philcs.	Eosino-philcs.	Large mono-nuclears.	Transi-tionals.
Before exposure	40	52	5	..	8	
Five days after	65	22	9	2	..	2
Nine days after	64	30	1	3		

Microscopical Sections. Stomach and remainder of gastro-intestinal tract negative; kidneys anemic, slight degree of desquamation of epithelium in proximal and distal convoluted tubules; spleen not decreased in size, splenic corpuscles show slight hyperplasia; no evidence of increase in fibrous tissue, of a coagulation necrosis; chromatin material of the follicle cells is broken up into fine granules. Nuclear membranes intact. No increase in mitotic figures; pulp has no anemic appearance. There is a marked increase in the blood pigment; immature white cells, myeloblasts, large cells with pale vesicular nuclei and plasma cells are quite numerous. In the liver the striking feature is the washed-out appearance of the parenchymal cells and an absence of the usual abundant granular cytoplasm. It appears as if there had been

an unusually great demand on the glycogen content or else the glycogen had been liberated by the action of some ferment. The hepatic cells are much enlarged. The nuclei also are considerably swollen; the Kupffer cells showed a hyperplasia and in many places lay free in the liver sinusoids. These, together with the hepatic cells themselves, contained an abundance of hemosiderin.

Sacrificed at 11.00 A.M., April 28. Animal active and normal, save for slight infection along line of incision.

Autopsy. Stomach is distended with food, but apparently normal; small intestine apparently normal, but not particularly friable and thin; no evidence of hyperemia; large intestine normal; the spleen is of normal size and of pale color; the liver has a somewhat greasy feel. Kidneys appear normal; also thorax, lungs and heart.

TABLE III.

(SR 3, white, spleen rayed fifteen minutes.)

Date.	Days after radiation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks
Before	...	1.58	8,000	4,768,000	400, carrots	350	Operation at 10 A.M.; the spleen rayed 15 min.
April 18	400, turnips	..	
19	1	400, carrots	..	Animal active.
20	2	1.49	6,800	4,448,000	430	
21	3	1.51	400, cabbage	280	Apparently normal.
22	4	400, carrots	320	
23	5	1.44	11,400	4,224,000	550, cabbage	345	No evidence of infection.
24	6	...	12,000	...	200, turnips	340	
25	7	1.49	11,800	...	400, turnips	400	Normal.
26	8	400, turnips	300	Normal.
27	9	1.50	9,000	4,096,000	400, carrots	430	Incision healing nicely.
28	10	...	6,600	...	400, cabbage	525	
29	11	1.53	10,000	

DIFFERENTIAL COUNT.

	Neutrophiles.	Lymphocytes.	Basophiles.	Eosinophiles.	Large mononuclears.	Transitionals.
Before exposure	38	50	3	1	8	
Five days after	35	54	3	5	3	
Nine days after	53	34	8	4	..	1

Microscopical Sections. Kidney shows a slight chronic passive congestion and cloudy swelling. Stomach, lower ileum and colon are normal; follicles of spleen show a slight hyperplasia with breaking-up of the chromatin of the cells into granular form; nuclear membranes are intact and the cells themselves somewhat swollen;

moderate amount of hemosiderin is found throughout the pulp, the reticular tissue of which shows no evidence of destruction or hyperplasia; spleen is somewhat anemic, but shows no evidence of infarcts; a few immature white cells are found throughout the organ. The paucity of the cytoplasmic granules of the liver cells which are somewhat enlarged, the pale color of the somewhat swollen nuclei, and the presence in the liver of leukocytes, whose chromatin has been broken up, and of a slight increase of the hemosiderin content are the noteworthy features.

Animal sacrificed at 10.00 A.M., Sunday, April 29. Air injected into marginal ear vein. Incision shows no evidence of infection.

Autopsy. Spleen seems normal in size, perhaps a trifle smaller than usual, and organ is of pale color; the liver is very large and pale; kidneys, gastro-intestinal tract, lungs and heart appear normal.

TABLE IV.

(SR 4, gray-white, spleen rayed fifteen minutes.)

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 18	...	1.36	8,200	5,056,000	400, carrots 300, turnips	460 ..	Operation at 11 A.M.; the spleen rayed 15 min.
19	1	400, carrots	..	
20	2	1.28	6,800	4,448,000	400, carrots	320	Active.
21	3	1.35	5,400	...	400, cabbage	400	Active.
22	4	400, carrots	285	Incision shows no sign of infection.
23	5	1.28	6,000	4,608,000	530, cabbage	500	Normal.
24	6	...	6,400	4,800,000	400, turnips	420	Normal.
25	7	...	5,800	...	400, turnips	..	No infection.
26	8	1.40	5,400	4,576,000	400, turnips	380	Normal.
27	9	400 carrots	..	Normal.
28	10	1.44	6,000	...	400, cabbage	460	Normal.
29	11	...	7,600	4,768,000			

DIFFERENTIAL COUNT.

	Neutrophiles.	Lymphocytes.	Basophiles.	Eosinophiles.	Large mononuclears.	Transitionals.
Before exposure	44	40	4	3	5	
Five days after	16	72	4	8		
Ten days after	50	46	..	2	2	

Microscopical Sections. Kidney is somewhat anemic; desquamation here and there of the epithelium lining the proximal and distal convoluted tubules; no evidence of a capilloglomerulo nephritis; gastro-intestinal tract is normal; spleen is somewhat bloodless,

the splenic corpuscles are slightly enlarged, there is no evidence of nuclear fragmentation, the nuclear membranes are intact, but the chromatin material is broken up into spherical granules of varying size; immature white cells are quite numerous; there is no evidence of fibrosis or destruction of lymphatic tissue. The liver cells are swollen and present a washed-out appearance; hemosiderin is present in abnormal amount; the sinusoids contain detached Kupfer cells, large mononuclear, and a few cells apparently washed over from the spleen whose chromatin has been broken up into granules.

Air injected into marginal ear vein, 11.00 A.M., Sunday, April 29.

Autopsy. Incision healing; no evidence of infection. Spleen of normal size and consistency; pale color. Liver has a somewhat greasy, soft feel; enlarged and pale. Stomach is slightly more pale than usual and distended. Intestine normal. Lower ileum shows no evidence of hyperemia, desquamation of the villi or ulceration. Kidneys, heart and lungs appear normal.

TABLE V.

(SR 5, white, spleen rayed fifteen minutes.)

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 18	...	1.57	8,800	4,704,000	400, carrots 300, turnips	250 ..	Operation at 12 m; spleen rayed for 15 min.
19	1	1.52	8,400	4,320,000	400, carrots	..	
20	2	...	6,400	...	400, carrots	300	Active.
21	3	400, cabbage	420	Active.
22	4	1.57	...	4,032,000	400, carrots	185	Active.
23	5	...	6,800	...	600, cabbage	400	} Apparently normal.
24	6	400, turnips	360	
25	7	...	8,800	...	400, turnips	320	No infection; apparently normal.
26	8	1.62	9,800	3,808,000	400, turnips	410	} Apparently normal.
27	9	400, carrots	205	
28	10	...	9,600	...	400, cabbage	300	
29	11	1.62	11,200	4,384,000			

DIFFERENTIAL COUNT.

	Neutrophils.	Lymphocytes.	Basophiles.	Eosinophiles.
Before exposure	50	40	9	1
Ten days after	52	42	6	

Microscopical Sections. Gastro-intestinal tract negative; kidneys somewhat bloodless; desquamation of a few of the cells lining the convoluted tubules. Spleen normal in size; slight increase in the

hemosiderin content; no evidence of fibrosis; chromatin material of the leukocytes and lymphocytes broken-up into spherical granules. Liver cells show a marked decrease in the glycogen content. Many of the stellate cells lie free in the liver sinusoids.

Air injected into marginal ear vein, 12.00 A.M., April 29.

Autopsy. No evidence of infection along line of incision. Spleen and liver of pale color; latter organ somewhat enlarged; spleen of normal consistency. Other viscera negative.

Microscopical Sections. Hyperplasia of splenic corpuscles; no increase in the connective tissues; few mitotic figures; chromatin broken up into granules; nuclear membranes intact; few immature white cells are found. Liver is slightly congested; hepatic cells swollen; paucity of their protoplasmic granules is especially noticeable; evidence of increased hemosiderin content. Kidneys show slight degeneration in the convoluted tubules.

TABLE VI.

(SR 6, gray, spleen rayed fifteen minutes.)

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 18	...	1.37	8,800	5,472,000	400, carrots	310	
	300, turnips	..	Spleen rayed 15 min.
19	1	1.23	9,000	...	400, carrots	240	Very active.
20	2	4,640,000	400, carrots	185	Very active.
21	3	400, cabbage	250	Very active.
22	4	400, carrots	360	Normal.
23	5	1.21	7,400	4,128,000	600, cabbage	320	Normal.
24	6	...	7,600	...	400, turnips	285	Normal.
25	7	...	6,200	...	400, turnips	..	Normal.
26	8	1.26	...	4,608,000	400, turnips	..	Normal.
27	9	...	7,200	...	400, carrots	420	Normal.
28	10	400, cabbage	..	Normal.
29	11	1.31	7,800	4,704,000	310	

DIFFERENTIAL COUNT.

	Neutrophiles.	Lymphocytes.	Basophiles.	Eosinophiles.	Large mononuclears.
Before exposure	44	47	4	..	5
Four days after	30	62	4	2	2

Sacrificed at 1.00 P.M., April 29.

Autopsy. Incision healing nicely. Spleen and liver are of pale color and of normal consistency; liver somewhat enlarged. Other viscera apparently normal.

Microscopical Sections. Gastro-intestinal tract is perfectly normal. Kidneys are somewhat bloodless and show slight degeneration in the convoluted tubules. Spleen is normal in size and shows

a slight enlargement of the splenic corpuscles; no changes are found in the reticular tissue framework. The thread-like chromatin material which normally connects the lobes of the polymorphonuclear cells is in many instances not to be seen; many of the cells show complete subdivision into three to six separate segments; the chromatin material of the lymphocytes is in many instances broken up into clumps of granules. The swollen empty liver cells contain here and there traces of blood pigment; many white cells in an early stage of degeneration apparently transported from the spleen are to be found in the liver sinusoids.

TABLE VII.

Control No. 1, dark gray.

Date.	Days after operation.	Weight, kilo.	White blood cells.	Red blood cells.	Diet, gm.	Urine, cc.	Remarks.
Before April 18	...	2.89	8,200	5,152,000	400, carrots 300, turnips	245 ..	Spleen pulled out on abdomen 15 min.
19	1	2.88	10,200	5,536,000	400, carrots		
20	2	...	10,000	...	400, carrots	280	Active.
21	3	...	12,600	...	400, cabbage	200	Active.
22	4	2.86	11,400	4,768,000	400, carrots	330	Active.
23	5	...	10,000	...	600, cabbage	380	Incision healing.
24	6	...	9,600	...	200, turnips	..	
25	7	...	8,200	...	300, turnips	..	
26	8	2.82	8,000	...	400, turnips	..	
27	9	...	8,600	5,440,000	400, carrots	215	
28	10	...	9,800	...	400, cabbage	..	
29	11	2.85	9,000	240	

DIFFERENTIAL COUNT.

	Neutrophiles.	Lymphocytes.	Basophiles.	Eosinophiles.	Large mononuclears.
Before operation . . .	43	51	5	1	
Five days after . . .	64	30	2
Ten days after . . .	49	47	2	..	2

Autopsy (2.00 P.M.). Incision healing nicely. Viscera appear normal; liver, however, seems slightly congested.

Microscopical Section. Slight chronic passive congestion in the liver and kidney; kidney sections revealed a desquamation here and there of the epithelium lining the convoluted tubules.

Control rabbit No. 2 died the day following operation. A few hours previous to death there was a marked retraction of the head and inactivity shown by the animal.

Control rabbit No. 3 presented no postoperative points of note that differed in any way from those of Rabbit No. 1.

Discussion. In our preliminary work on Series 1 and 2 we were able to produce the typical clinical symptoms of roentgen-ray intoxication by exposing the abdomen to a lethal dose of roentgen-rays. These symptoms made their appearance on the eighth day and, increasing in severity, terminated in the death of the animal on the eleventh day. Sections of the lower ileum revealed a hemorrhagic mucosa denuded of its villi as reported by other investigators. The animals of Series 3, on the other hand, the spleens of which were exposed to the same lethal dose of roentgen-rays, showed no apparent clinical symptoms of a systemic intoxication during the eleven days following exposure. All the rabbits, except one of the controls which died the day following operation and SR 2 which showed a slight local infection, made excellent recoveries from the effects of operation. Though a slight loss of weight was in evidence for a few days following operation, this was in part due to the fact that the animals were starved before operation and in part due to the operation itself, as shown by a loss of weight also in the controls. White-blood counts of the animals, the spleens of which were rayed, were slightly below normal; the controls, on the other hand, showed a slight postoperative leukocytosis. The fact that the leukopenia in the "spleen-rayed" animals was only of slight grade is not insignificant if one bears in mind the fact that we are here dealing with a combination of factors: Operation with its usual postoperative leukocytosis and the effect of roentgen-rays on the leukopoietic organ. If we consider the spleen-rayed rabbits to have a normal count of 11,000 to 12,000 (due to a factor of operation) and find a count of 10,000 or less following exposure, we may attribute that to the effect of the roentgen-rays.

In all the spleen-rayed animals there was evidence of destruction of red cells, as shown not only by the lowered red counts but also by the hemosiderin content of the spleen and liver. No erythroblasts were found in the blood smears. Differential counts taken four days after radiation of the spleen showed in all cases, except SR 2, a decrease in the number of leukocytes per 1 cm. of blood with a relative lymphocytosis; the percentage of eosinophiles was somewhat high (10 per cent) in SR 1, the spleen which received a ten-minute exposure. It is rather significant that the spleen and liver of this same rabbit showed a greater content of hemosiderin than that of any other rabbit; ten days following exposure we find an approach to the normal differential count. A blood smear from SR 3 at this time showed the presence of an occasional Türk's irritation form, regarded as a product of the irritation of the bone-marrow.

The question is what factors determine the number of different cells in the circulation. Why should we not expect to find irritation forms in the other blood smears, and evidence of a more marked

destruction of red cells in those animals exposed for the longer period of time than we found in the case of SR 1, etc.? It is well known that individuals with normal blood counts react differently in the number of cells thrown into the circulation in response to some pathological condition. So here, with the exposure of the spleen alone to an amount of roentgen-ray energy far short of the minimum lethal dose, in only part of the animals might we expect this effect to be evidenced. Taylor, Witherbee and Murphy⁷ claim there is a fluctuation in the percentage of lymphocytes in the blood stream following roentgen radiation. They maintain there is a sudden decrease in the circulating lymphocytes following roentgen radiation; this is followed by a rise and then another fall; this is in turn followed by a rise and again a fall in the percentage of lymphocytes.

Anatomical changes are not very conspicuous in the animals, the spleens of which have received a lethal dose of roentgen-rays. On the eleventh day following its exposure to a lethal dose of roentgen-rays we found in the spleen no evidence of fibrosis and no areas of caseous necrosis or anemic infarctions associated with thrombosis of the splenic vessels. Hemosiderin was present, however, in somewhat increased amount; mitotic figures were few; the cells of the splenic corpuscles, however, the small and large lymphocytes and the large mononuclears and, to some extent, the polymorphonuclears of the pulp immediately adjacent to the follicle, showed a beginning degenerative change. The protoplasm showed no changes whatsoever; the nuclear membranes were preserved, but the nuclei were swollen and their chromatin material broken up into spherical granules of varying sizes. The delicate thread-like chromatin material which normally connects the lobes of the polymorphonuclear cells was in many cases not to be seen. These changes had not taken place in the control animals.

Heineke⁶ found degeneration of the lymphoid follicles in the spleen following roentgen-ray exposure; he noticed a fragmentation of the tissue lymphocytes, mitotic figures were absent and the lymph follicles inconspicuous; the stroma was much in evidence, owing to the destruction and consequent disappearance of lymphogenic cells. Warthin⁴ claims that the changes in the lymphoid organs following roentgen-ray exposure come on slowly: cells do not show marked advanced stages of degeneration until ten to fourteen days after the irradiation. The injured cells then split up into fragments, all traces of protoplasm are lost and only chromatin granules remain as chromatin dust. This injury, he continues, is not a diffuse one. Only certain cells, apparently, are affected, as many cells apparently normal are found near degenerating cells. Warthin, it must be remembered, was dealing with the effect produced by roentgen-rays on the lymphoid organs of leukemic individuals.

The striking feature in the case of our liver sections was the large hepatic cells with swollen nuclei devoid of their usual abundant granular cytoplasm. Either a great demand had been made upon the supply or some agent had hastened the transformation of glycogen into sugar; as a matter of fact, the circumstances and exact control of such a change under normal circumstances has not been satisfactorily made clear as yet. It is known, however, that depriving the liver of its oxygen supply leads to the conversion more or less complete of glycogen to sugar; the process can be hastened by the stimulation of the splanchnics. Carbon-monoxide poisoning leads to the discharge of the glycogen; chloroform and some other anesthetics easily produce glycosuria in rabbits and dogs.

Our control animals showed that only a slight, almost inappreciable, amount of liver glycogen had been converted into sugar, while in the case of the spleen-rayed animals there was a total absence of glycogen in the liver cells; this would tend to rule out the factor of anesthesia. Is it possible that by exposure of the spleen a glycogenolytic enzyme is set free or that toxic split products are formed which favor the conversion of glycogen to sugar without affecting in any way the cell membrane or nucleus? That there was a response to a toxin of some sort on the part of the liver in the rayed animals was shown by the swelling, hyperplasia and desquamation in places of the Kupfer cells. Hemosiderin was present in the liver in varying amounts over the normal content.

Sections taken from the stomach, lower ileum and colon appeared normal. The kidneys, on section, appeared somewhat bloodless and showed only a slight amount of desquamation of the epithelium lining the convoluted tubules; this same desquamation was, however, found in the controls. This desquamation may be interpreted as evidence of the secondary nature of roentgen-ray action on the kidney since that organ was not in the path of direct-ray action.

Summary. The lethal dose of roentgen-rays used in these experiments invariably produced a systemic intoxication and resulted in death on the eleventh day following exposure of rabbits over whose lower abdomen or left hypochondrium it was applied.

Direct radiation of the spleen with this same lethal dose, however, gave rise to no apparent clinical symptoms. At the end of the eleventh day the rabbits whose spleens were rayed were acting essentially like normal rabbits.

There was a fall in the white-blood count characterized by a relative lymphocytosis five days after raying and a return to an approximately normal differential count five days later. A few Türck's irritation forms were found in one of the rabbits ten days after exposure of its spleen. The lower red-blood counts and the

increased hemosiderin content of the spleen and liver gave evidence of increased red-blood-cell destruction.

The only findings at autopsy were a pale looking spleen and a large pale liver; the spleen showed no evidence of fibrosis; no areas of caseous necrosis. An early stage of chromatolysis was found, however, as shown by the breaking-up of the chromatin material of the large and small lymphocytes into granules of varying sizes and the absence in many instances of the delicate chromatin thread which normally connects the nuclear lobes of the polymorpho-nuclear cells. The chief features of the liver sections were the washed-out appearance of the liver cells, the hyperplasia and desquamation of the Kupfer cells and the abnormal hemosiderin content.

Our experiments gave no evidence of injury to the gastro-intestinal canal; the slight amount of degeneration found in the convoluted tubules of the kidney was also found in the controls. This is of importance in the interpretation of the work of Hall and Whipple. The theory that foci of necrosis occurring in the intestinal wall after general radiation are caused by the elimination of toxicous split-products seems to be untenable, at least so far as the spleen is concerned. Rather, such evidence of injury, together with similar effects produced in the kidney, would seem to be referable to the direct action of the rays.

In conclusion, I wish to acknowledge with sincere appreciation the use of facilities placed at my disposal by Dr. W. P. Davey of the Research Laboratory of the General Electric Company at Schenectady.

REFERENCES.

1. Hall, C. C., and Whipple, C. H.: Roentgen-ray Intoxication, *AM. JOUR. MED. SCI.*, 1919, 157, 453.
2. Martin, Charles L., and Rogers, Fred T.: Intestinal Reaction of Erythema Dose, *Am. Jour. Roentgenol.*, 1923, 10, 11.
3. Edsall, David L., and Pemberton, Ralph: Toxic Reaction and the X-rays, *AM. JOUR. MED. SCI.*, 1907, 133, 286, 426.
4. Warthin, A. S.: *AM. JOUR. MED. SCI.*, 1907, 133, 736.
5. Rosenstein, J.: *München. med. Wehnschr.*, 1906, 53, 1009.
6. Heineke, H.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1905, 14, 21.
7. Taylor, Hubert D., Witherbee, William D., and Murphy, James B.: Destructive Action on Blood Cells, *Jour. Exper. Med.*, 1919, 29, 53.

THE ATYPICAL SPINAL TUMOR.

. BY NORMAN SHARPE, M.D.,

NEW YORK.

SPINAL tumors, directly or indirectly involving the cord, so often exhibit a similarity of symptoms and signs that a tumor syndrome has been evolved. This syndrome is composed first of pain and paresthesia, followed by muscle paresis, varying stages of anesthesia, muscle paralyses and impairment to even loss of sphincteric control.

Excepting neurologists and others who frequently encounter spinal tumor, it is rather generally taken for granted that practically all new growths about or in the cord will give rise to the group of symptoms and signs in the order given above. This is by no means the case.

Since the larger number of spinal tumors are situated posteriorly to the cord, the sequence of development of the cord signs noted above can be readily understood. As the tumor develops, first it irritates and compresses a sensory nerve root or roots and the adjacent ganglia, giving rise to pain and paresthesias in the area of distribution of the affected root. As the tumor enlarges, the motor tracts become compressed, causing muscle paresis, spastic in type if the tumor is located above the lumbar enlargement of the cord, atrophic in type if the tumor is situated at or below the lumbar enlargement. Later, with further growth of the tumor, more severe compression causes paralyses, anesthesia and sphincteric loss.

This so-called "typical" spinal-cord tumor syndrome is widely known, and when a tumor follows this "typical" course the condition is usually rather easily diagnosed.

It is less widely known that very many spinal tumors do not follow a "typical" course, do not even closely approximate the features of the tumor syndrome outlined above. Some of the supposed leading signs of tumor may be omitted, and the sequence of the signs of the "typical syndrome" be distorted or reversed. Very often this is due to the situation of the tumor, lateral or anterior to the cord. But often the development of the cord signs is difficult of analysis, even after the condition is disclosed at operation. Still less well known is the fact that spinal tumor may not only not follow a "typical" course, or not even an "atypical" course, but may so closely simulate some organic cord disease as to deceive the very elect. By the term organic cord disease is meant such conditions as multiple sclerosis, syringomyelia, myelitis, etc. It is not difficult to conceive of the signs of tumor simulating those of cord disease in the neighborhood of the lesion, but the

presence in tumor cases of symptoms in distant portions of the nervous system are difficult of explanation except upon the basis of toxins generated by the growth. The simulation of cord disease by tumor may exist not only in the beginning, but may be carried well on into the course of the new growth.

From what has been said above, it will be seen that the generally accepted idea that a "spinal-cord tumor syndrome" exists is unfortunate. The belief that cord tumor develops a universal syndrome with an orderly sequence of signs has led to many errors and delays in diagnosis, with the result that operative measures are withheld until the cord has often been irreparably damaged. Surgical treatment of cord tumors has only been employed for the last thirty years, and in the early years operation was performed only when undoubted tumor signs were present, the "typical tumor syndrome" referred to before. In consultations on spinal lesions it is not seldom that one hears the remark that, "As there has been no pain of any kind, we can safely rule out cord tumor." Of course, neurologists and others seeing many cord tumors know that these growths very often do not give rise to a "typical" and orderly sequence of symptoms and signs, *i. e.*, pain and paresthesia, muscle palsies and anesthesia. Of the tumors involving the cord that have come under my observation, more than half were "atypical" in their development, in that the symptoms and signs did not correspond, at least in some leading sign or signs, to the above formula. And others closely resembled some well-recognized form of organic cord disease.

The four patients whose histories are reported below were chosen because their lesions illustrate how atypical the course of cord tumor may be. Two had extradural tumors, involving the cord; 1, an intramedullary tumor; and 1, a pseudotumor (circumscribed serous meningitis). All of these lesions show features at variance, sometime widely, with the generally accepted behavior of cord tumor. In these case reports all the negative findings are omitted, except those having a distinct bearing on the condition.

While it is recognized that one should be careful in drawing deductions from a single case, yet it is felt that a discussion of these individual conditions may add to our knowledge of the variegated signs that these, at times puzzling, lesions may present.

CASE I.—C. R., aged twenty-eight years. In July, 1918, after having been under a severe strain nursing her mother, who died of cancer in June, she complained of tremors and weakness in the legs after exertion. These symptoms gradually grew more marked, and when, in October, 1918, she noticed tremor of the hands when fatigued she went to a clinic for examination. A diagnosis of multiple sclerosis was made. Two months later examination in another clinic yielded the same diagnosis. I first examined her in January,

1919, in a third clinic. Her condition was as follows: She walked with stiff spastic gait and tired quickly. Both legs were spastic; knee- and ankle-jerks exaggerated; double ankle clonus and double Babinski elicited; upper abdominal reflexes present, lower absent. Tremor of hands, intention in type; lateral nystagmoid twitching of both eyes; no pallor of optic disks. Sphincters not impaired, and no tenderness to pressure over the spine. Tests showed no impairment of sensation. The patient said that there had been no pain at any time.

Diagnosis: Multiple sclerosis. Examined again in July, 1919; her condition was the same, except that it was more difficult for her to get about. Lumbar puncture at this time yielded a clear fluid under normal pressure, normal cell count, normal globulin, albumin not present and the Wassermann reaction negative.

The patient was lost sight of until January, 1920, when I found her completely paralyzed below the waist. She said that the stiffness and the weakness of the legs had gradually increased from July, 1919, on until November 1, when she was unable to move them at all. A month later, in December, 1919, she had complained of numbness and tingling in the legs, and this had gradually grown more marked. The examination in January, 1920, showed marked sensory impairment below the level of the tenth thoracic cord segment (1 to 2 inches below the umbilicus). There was marked hypesthesia to all forms of sensation below this level, with scattered areas of complete anesthesia over thighs and legs. Touch better maintained than pain or thermal sense. No sphincter impairment. No tenderness over the spine, and skiagraphs revealed nothing definite. The former tremors of the hands and the nystagmoid twitchings of the eyes not present now. The picture was now one of tumor, not multiple sclerosis.

Laminectomy was performed February 5, 1920, of the sixth to the ninth thoracic vertebrae. The left lamina of the seventh vertebra was partly eroded, and an encapsulated egg-shaped tumor, $1\frac{3}{4}$ inches long and 1 inch in diameter, was found in the canal in front and to the left of the cord. The lower pole of the tumor had eroded the posterior wall of the foramina, flattening the nerve roots. The cord was markedly flattened against the posterior wall of the canal. The tumor was rather easily removed from its bed and peeled from the dura. Eight days after operation the patient could flex and extend legs and lift the feet. Sensory impairment less. Three weeks later the patient could walk by holding. Two months after operation she walked several blocks without fatigue, and sensation was normal. Clonus and Babinski signs still present. Three months later she returned to her work; could dance and get about as well as before illness. At the present time, three years after operation, she remains well and strong. The knee-jerks are slightly plus and an inconstant Babinski occasionally found.

Pathological report on tumor: One laboratory found it to be "a benign tumor of indefinite origin and type," while a second laboratory stated that it was "an atypical spindle-cell sarcoma, with many giant cells, which had outgrown its blood supply."

The first point to be noted is the extraordinary stimulation of multiple sclerosis by the tumor signs. Spasticity of the legs is common both to sclerosis and to tumor above the lumbar enlargement; likewise loss of the abdominal reflexes. Nystagmus is a cardinal sign in multiple sclerosis; not at all a sign of spinal tumor. The nystagmoid twitchings found in this patient are difficult to explain. That they were due to toxins generated by the tumor (referred to earlier in the article) is hardly credible in this case, as the tumor was extradural. They were probably due to fatigue, for the patient had difficulty in walking and complained of fatigue on her visits to the clinic. Fatigue was probably the cause also of the hand tremor. Months afterward, when the patient was examined in bed, the nystagmus and hand tremor were absent. It may be contended that this was not a true nystagmus or a true intention hand tremor. Yet they were sufficiently life-like to lead three observers in different clinics to make a diagnosis of multiple sclerosis.

The absence of pain at any time during illness, while not unknown in cord tumor, was a difficult point to surmount in the consultation preceding operation. It was still more difficult to explain at operation, when the posterior wall of the eighth foramina was found eroded and the nerve root flattened to a ribbon. It can, however, be explained on a mechanical basis. As the tumor lay obliquely in the canal, if it grew from above downward, the erosion of the foramina and compression of the root was a late development. By this time the upper pole of the tumor had so compressed the cord as to prevent the passage upward of pain impulses.

The failure of the roentgen-ray to reveal the bone erosion previous to operation may be thought surprising, but really it is not so. On a skiagraph taken several weeks after the operation, with an open canal, the lines of erosion were only faintly discernible and could easily have been misinterpreted. Spinal roentgenograms are exceedingly difficult to "read," and usually are not of much help to the neurosurgeon unless there are alterations in the bony alignment. Roentgenograms should always be made, however, for they may unexpectedly throw light on the condition.

The late development of sensory impairment is rather remarkable, although the position of the tumor in front of the cord would call for tardy sensory disturbance. In view of the fact that at operation the cord was found markedly flattened against the bony canal, the late occurrence of sensory disturbance seventeen months after the onset of the illness and one month after complete motor par-

alysis is surprising. It confirms what was previously known, that sensory nerve fibers suffer compression with much more tolerance than do motor fibers.

The absence of sphincteric impairment, in view of the marked cord compression, is unusual. While the spinal centers for the sphincters are believed to be in the lumbar enlargement of the cord, yet with complete motor paralysis and partial sensory loss it would be supposed that the ascending and descending fibers to those centers would also be involved. I have seen at this level and higher up sphincteric disturbances and even loss of control in lesions apparently more moderate in their interference with the cord than this one. We can only assume that the fibers for the sphincters escaped compression, as some of the sensory fibers did, or that occasionally the spinal centers in the conus are capable of functioning independently.

The quick recovery of function was not only gratifying but striking. Although complete paraplegia had been present for three months before operation, yet eight days later she could move the legs, walk (weakly it is true) in three weeks, and two months after operation sensation was normal, and she could walk several blocks without fatigue. This illustrates again how tolerant the cord is to pressure gradually applied, in contradistinction to the results seen in sudden compression, as in fracture of the spine.

The negative findings in the fluid at lumbar puncture are those usually met with in extradural tumor with an intact dura. Negative findings are indicative of lack of inflammatory reaction within the dura, and can, with reservations, be used as a basis for prognosis of return of cord function. Conflicting and doubtful laboratory reports on cord tumors are not unusual. This is doubtless due to the relative infrequency of spinal tumor.

CASE II.—F. M., aged sixteen years. In 1916, when twelve years old, he was struck by a trolley-car, receiving severe bruises of the trunk and legs. He does not recall whether the back was injured or not. He was confined to bed and house for six weeks, and apparently completely recovered. He went to work when fifteen years old. In the autumn of 1919 he had mild shooting pains in the back of the legs, with occasional tenderness to pressure over the middle of the spine and pain in the back on bending. This continued intermittently until March 1, 1920, when he complained of "pins and needles" sensation in the legs and weakness in both knees. This weakness rapidly increased, so that in two weeks he was unable to walk. At this time there developed slight numbness of the legs to the groin and some hesitancy in bladder function.

When examined March 25, 1920, there was a complete flaccid paralysis of both legs to the groin, with the exception that he could weakly move the toes of the left foot. The knee and ankle

tendon reflexes were absent and there was marked atrophy of all the muscles to the groin. Tactile sense fully preserved, marked diminution of pain and thermal sense. No anesthesia. Muscles of both legs and thighs were markedly tender to pressure. Tenderness over spine from the eleventh thoracic to second lumbar vertebræ. There was an apparent backward curve of these spines, but skiagraphs showed nothing abnormal in spinal curve or vertebral outline. Control of bladder and rectal sphincters impaired but not lost. In the following days he complained of increasingly severe pain in the back and legs. Laminectomy was performed March 29, 1920. When the laminæ of the twelfth thoracic and first lumbar vertebræ were removed a dark red mass protruded, completely hiding the dura. Removal of the eleventh thoracic laminæ revealed a normal pulsating dura free of the mass, and removal of the second lumbar laminæ below disclosed the dura without pulsation. When the larger part of the mass, which was found to be laminated and partly organized blood clot, was stripped from the dura there was found beneath it a 1-inch wide collar of dense yellowish fibrous tissue completely encircling the dura and severely compressing it. Tedious dissection freed the dura, and on incising the ring of fibrous tissue pulsation returned in the dura below the lesion. Because of the amount of blood clot remaining in the canal, the dura was not opened and the wound was drained. A large amount of grumous blood escaped the following two days, and a low-grade suppuration occurred, which disappeared after several days.

Fifteen days after operation the patient could flex the left knee and foot and move the toes on the right foot. Three weeks later he could walk with assistance. Sensation and sphincters were normal. Nine months after operation he returned to work. The left leg was about normal in strength, the ankle-jerk normal and the knee-jerk feebly present. The right leg—strength fair, foot-drop, knee-jerk absent, and ankle-jerk feebly present. Exercises in the following months partially overcame the right foot-drop, so that at present dorsal flexion of the foot is only subnormal. Otherwise he is well and strong. The pathological report of the tumor was, "An endothelial angioma, springing from the connective tissue of the spinal canal." Doubt was expressed as to malignancy.

Following the onset of paraplegia and before the patient's admittance to hospital, two diagnoses had been made of his condition. One was multiple neuritis and the other transverse myelitis. Either was a likely diagnosis in view of the swift onset and rapid progression of the paralysis and the history then obtained. Although he was not unintelligent, it was only by persistent and leading questioning that the existence of leg pains and intermittent muscle weakness for a period of several months was brought out. Just as in brain

tumor the importance of the early signs, existing before the condition has become masked by increased pressure or by toxemia cannot be overestimated. It was the history of "pins and needles" sensations and occasionally muscle weakness persisting for five months, together with the tenderness over the spine, that decided for tumor and for operation.

The *conus medullaris*, the portion of the cord involved by this lesion, is most susceptible to injury, and complete recovery is the exception rather than the rule, even after moderate degrees of injury. Though in this patient the cord was found much less compressed, and had endured this for a much shorter time than was the case with the preceding patient, yet his recovery of full function was much slower. His quick initial recovery, he being able to walk unassisted in one month, was rather surprising. His later slow recovery was that more usually seen in *conus* injury.

Sphincter disturbance occurs early and constantly in lesions involving this portion of the cord. A hopeful sign in this patient's condition was that while the sphincters were impaired control was not lost. In conditions where operation reveals compression of the *conus* the degree of sphincter impairment can be used, and was in this case as a basis of prognosis of the patient's general recovery of function.

CASE III.—S. G., woodjoiner, aged thirty-one years. In September, 1917, an abscess developed in his left nostril. In the following three months abscesses successively appeared in the left orbit, on the left side of the face and later on the left side of the neck, 2 inches below the mastoid. All the abscesses were deep-seated and required a long time for healing, the last one closing early in January, 1918. A few days later pain and stiffness developed in the left side of the neck and he carried his head in a fixed position. At a clinic, to which he went, the diagnosis of cervical Pott's disease was made and a rigid helmet of leather applied and worn until July, 1918. During the preceding month of June he noticed numbness in the right hand and weakness of the left hand and arm. Two months later these signs had progressed to a spastic paralysis of the left arm and leg without sensory disturbances in these parts, associated with numbness and lowered sensation of the right half of the body, excluding the face. At a second clinic, in September, 1918, although two blood Wassermanns were negative and later two other blood Wassermanns and a spinal fluid Wassermann were negative, the condition was diagnosed as luetic bone disease, and arsphenamine was given intravenously several times without benefit. Four skiagraphs of the cervical spine taken during these weeks showed nothing abnormal. I saw him in November, 1918. He had spastic paralysis of the left arm and leg, with increased reflexes, ankle and patella clonus and Babinski sign present. He could

slowly and weakly flex the leg on the thigh and feebly flex the forearm, but could not move the fingers. Sensation of the left half of the body was normal. Over the right half of the body there was hypesthesia in large areas to all forms of sensation, but no actual anesthesia. The sphincters were not impaired. There was tenderness to pressure on the left side of the neck opposite the body of the third cervical vertebra and slight tenderness on the posterior wall of the pharynx at this level. At this examination a small sinus was found on the posterior pharyngeal wall directed toward the body of the third cervical vertebra, but skiagraphs showed nothing abnormal. As his condition had remained stationary for three months, I advised waiting for further development.

In January, 1919, he reported that he was losing power on the right side of the body. Examination confirmed this. Sensory disturbances were unchanged. A diagnosis was made of a lesion, nature unknown and affecting the cord at the level of the third cervical vertebra, and laminectomy was advised and performed, January 29, 1919. On removal of the third, fourth and fifth cervical laminae the dura was disclosed tense and distended, and indented on the left side by a small projection of bone from the body of the third cervical vertebra. A probe passed up and down the canal outside the dura found no other obstruction. The dura was smooth and normal in appearance. On opening the dura and arachnoid clear fluid spurted to a height of several inches for ten to twelve seconds, though the head and trunk were on a lower level than the operative field. The cord appeared normal and I was not able to identify any adhesions or sac wall that had retained the fluid.

Eight days after operation he could move the left fingers and hand more freely than for six months. He complained of paresthesia in the right hand and foot. Three weeks later he could raise the left hand above his head. A tiny fragment of bone was discharged from the pharyngeal sinus, which promptly healed. Three months later he walked well and wrote legibly (was left-handed). Ten months after operation he returned to his former work, which required good control over muscles and joints. He complained from time to time of paresthesia and pain about the scar. At the present time he is normal in strength and has been so for the past two and a half years.

There seems to be no reason to doubt that the lesion was a mild infection of the body of the third cervical vertebra, perhaps including one or two of the adjacent vertebrae, with subsequent inflammatory involvement of the arachnoid and pia at this level. This gave rise to adhesions which confined the cerebrospinal fluid—a circumscribed meningitis serosa. The paralysis and sensory disturbances were due to the pressure of the confined fluid and not to the exostosis found in the canal, which was small, and though it indented the dura, it did not press upon the cord.

The picture presented before operation was that of a lesion of one-half the cord—the left half; yet at operation the dura was distended equally in all directions, and on opening it the cord seemed to be lying in the center of the distended cavity. The left hemiplegia and right sensory disturbances indicate that the bulk of the fluid pressure was on the left side of the cord until the extension of the process involved also the right side, as was shown by the increasing motor impairment of the right arm shortly before operation. Had operation not been done, there can be no doubt that the patient would have become totally disabled within a few months.

The diagnosis of Pott's disease early in his illness is perhaps understandable, even though the skiagraphs showed nothing abnormal, for in cervical Pott's disease there is, as a rule, but little bone destruction. But the diagnosis of syphilitic bone disease and the repeated administration of arsphenamine intravenously, in spite of the repeated negative blood and spinal-fluid examinations, can scarcely be defended. This is a procedure all too common the last few years.

The history of this patient demonstrates again what some of us have been urging—namely, the value of exploratory laminectomy in progressive lesions involving the spinal cord, even though a diagnosis cannot be made, if the lesion has crippled or threatens to disable the patient. Naturally this does not mean that well-known clinical forms of cord disease that have some aberrant or unusual symptoms or signs should be operated upon. But these patients should be kept under suspicion and observation. Nor does it imply immediate operation on non-diagnosed lesions, especially if the signs of cord involvement are stationary. It is wiser to await further development. It may be safely taken as a rule, that cord lesions that can be helped by operation will not long remain stationary. Before the operation on this patient I thought the lesion might be a thrombosis of the vessels of the cord. But as I could not be positive, operation was urged, with the result that this patient was restored to normal health and usefulness.

CASE IV.—M. N., aged fourteen years. When seven months old a small lump was removed from the soft parts over the sacrum. When an infant a soft doughy mass was noticed over the spine between the scapulæ. This had remained stationary in size until the summer of 1921, twelve years later, when it began to enlarge. Seen in February, 1922, the patient's history was that five months previously there was noticed some loss of power in the left leg, and two months later slight weakness of the right leg, accompanied by pain in both shoulders and weakness of the left arm. The weakness of the legs gradually increased, so that in January, 1922, she had difficulty in walking; also some loss of bladder control, which had been present for two months.

Status in February, 1922: Both legs were spastic, with increased tendon-jerks, double Babinski and left ankle clonus. Dorsal flexion of the left foot was very weak, but the patient could walk a short distance unassisted. Both abdominal reflexes were feebly present. There was hypesthesia to touch, pain and thermal sense over the legs and trunk up to 2 inches below the clavicle in front and to the scapular angles posteriorly, pain and thermal sense being more affected. The muscles over both shoulders were tender to pressure, especially on the left side. The left-hand grasp was very weak, with marked atrophy involving the last two fingers and the small hand muscles, with anesthesia in the ulnar distribution of the hand and hypesthesia, extending for several inches upward on the inner side of the forearm (8 C and 1 D). Over the spine, extending from the seventh cervical spine to the third thoracic spine, was a soft, doughy mass adherent to the skin but freely movable otherwise—a lipoma. The patient stated that this had been getting larger the last seven months. Skiagraphs showed nothing abnormal in bone outline. She had some slight difficulty in controlling the bladder. At lumbar puncture the spinal fluid was found clear under normal pressure; cells, 6 per cm.; globulin and albumin were present in faint traces; the Wassermann was negative.

The tentative diagnosis was spinal gliosis, a syringomyelia, but the patient was kept under observation. By the middle of April, 1922, the spasticity of the legs and sphincter disturbances had become more marked, with increasing weakness in the left hand and forearm. She complained of increasing pain in the shoulder. Sensory impairment was unchanged, except that a narrow zone of hyperesthesia had appeared at the upper margin of sensory loss.

The diagnosis was made of intraspinal growth, probably a lipoma. Operation was advised and performed April 28, 1922. On removal of the seventh cervical, and first and second thoracic laminae, the dura was found tense and bulging. Incising the dura, a growth 2 inches long and $\frac{1}{2}$ inch wide was found firmly attached to the posterior surface of the cord, or at least to the pia. It was yellow in color and in consistency closely resembled the superficial lipoma. The growth did not appear to penetrate the cord, but it was so firmly adherent that dissection would have meant grave cord injury. The wound was sutured, the dura being left unclosed to permit separation of the growth from the nerve structure.

One week after this operation the spasticity of the legs was much lessened, bladder sphincter control was normal, the hyperesthetic zone about the shoulder girdle had disappeared and sensation in the left hand, trunk and legs was much improved. One month after the first operation the wound was reopened. The tumor was found to have greatly enlarged, requiring removal of the sixth cervical laminae to expose its upper pole. The lower pole extended to the second thoracic vertebra, more than doubling its former

length, and it was twice the former width and thickness. The growth could not be freed from the cord at any point, and careful rotation revealed penetration of the cord substance. A small section removed for examination was reported by the laboratory as "a fibrogloma," the section containing much fibrous tissue probably derived from the meninges.

Based on the rapid progress of the growth, the prognosis was made that the patient would die or be totally disabled within six months. But the patient held the improvement gained after the first operation for a period of three months; she was able to walk a few steps, had control of the sphincters and sensation was almost normal. Then retrogression occurred in motor power, the right arm also becoming weak, with weakness and atrophy of the hand muscles. Her status in January, 1923, was as follows: Slight pain in the right shoulder, weakness of both arms but no paralysis, with atrophy of the small muscles of both hands. The only sensory impairment found was slight hypesthesia to touch. There was spasticity in both legs, with double clonus and double Babinski. She could flex, extend and raise legs, but could not walk or stand alone. Sphincters were impaired, but control was not lost. As her condition had remained unchanged during the previous three months, there was a possibility that retrogression had occurred in the tumor itself, or that it had, partially at least, freed itself from the cord. Reoperation was advised but was refused.

The diagnosis of tumor was not made at the early examinations. The history, the symptoms and the signs pointed rather to a gliosis or syringomyelia of the lower cervical cord, the usual site for this disease process. The only dissonant note in this diagnosis was the presence of pain in the left shoulder and arms, and it was this that led to the lumbar puncture and to keeping the patient under observation.

Also because of the presence of the superficial congenital lipoma upon the spine, a spina bifida occulta was suspected, for as has been shown in a previous article¹ 50 per cent of this type of spina bifida are accompanied by overlying lipomata. But skiagraphs showed the bony canal to be intact.

With the development of the hyperesthetic zone above the skin level of sensory loss the diagnosis of tumor was made. As the superficial lipoma had begun to grow only a few months before the onset of cord signs, it was thought that the spinal tumor was also a lipoma, either intra- or extradural, tissue that had been pinched off from the superficial lipoma by the closure of the spinal canal in fetal life.

Though we were fairly certain in deciding to operate that the condition was one of tumor, had it proved to be syringomyelia with

¹ Sharpe: Spina Bifida, Ann. Surg., 1915, 61, 151.

cavity formation the operation would not necessarily have been without benefit. For it has been shown that a syringomyelic cavity can be drained with marked benefit to the patient.²

The rapid growth of the tumor during the four weeks' interval between operations was most surprising. It was doubtless due to the extra space provided by the laminectomy and opened meninges. Had the time interval been shorter the tumor would, of course, have been much smaller, but equally irremovable. It is usually considered advisable in two-stage operations for adherent spinal growths to perform the second stage after an interval of seven to ten days. This I regard as much too short a time. It is almost impossible to obtain an aseptic operative field in this time. If the wound is allowed to heal completely, which will require from three weeks to a month, not only will the chances of asepsis be better, but the longer time will allow the cord to more completely free itself from the growth. Even though the longer interval allows the growth to attain much greater size, if it has freed itself from the cord removal is not made more difficult.

Summary. There are many spinal tumors that do not, in their symptoms and signs, correspond to the syndrome that is generally accepted as indicating the presence of these growths. Many times this is due to the unusual position of the tumor. Often it is due to causes that are difficult of analysis, even at the time of operation.

Occasionally a spinal neoplasm for a considerable period of its development will exhibit symptoms and signs closely simulating those of some organic cord disease, such as myelitis, multiple sclerosis and syringomyelia. Eventually, however, the tumor will betray its presence, if the observer be alert, by the development of symptoms and signs foreign to those of cord disease.

Any condition regarded as organic cord disease that possesses any symptoms or signs not common to that disease should be kept under observation and frequently examined for the appearance of tumor signs.

As the majority of spinal tumors are removable, and if operation be performed early, most tumor patients can be restored to normal or near normal, it is of the utmost importance that diagnosis be made early, and also that tumor be not allowed to masquerade as cord disease for want of frequent examination.

As most organic cord diseases are chronic and progressive affairs on which treatment has but little effect, it is better in doubtful cases in which tumor is suspected to operate and occasionally find cord disease which will not be helped by the operation than it is to overlook, for want of operation, a tumor that will in its progression cause irreparable damage to the cord.

² Sharpe: Spinal Decompression, *AM. JOUR. MED. SCI.*, 1919, 158, 325.

THE DIETETIC MANAGEMENT OF DIABETES.*

BY FREDERICK M. ALLEN, M.D.,

MORRISTOWN, N. J.

(From The Physiatrie Institute, Morristown, N. J.)

I SHALL try to develop briefly three propositions:

- I. TREATMENT BY INSULIN AND PROPER DIET CONTROLS EVEN THE SEVEREST CASES OF DIABETES.
- II. REGULATION OF TOTAL CALORIES AND BODY WEIGHT RETAINS ITS IMPORTANCE AS THE BASIC PRINCIPLE OF DIET.
- III. INCORRECT DIETS ARE DANGEROUS IN DIABETES WITH OR WITHOUT INSULIN.

I. Results of Treatment by Insulin and Proper Diet. We are now on the high tide of enthusiasm over the monumental discovery of insulin by Banting and his collaborators, and there will scarcely be any dispute of the statement that patients with the most severe and hopeless diabetes can by this means be miraculously restored in weight, strength, comfort and usefulness. Ourselves and others¹ have published abundant records of such cases, and a few of the photographs are reproduced here as examples (Figs. 3 and 7). Only the grossest mismanagement of diet can prevent these wonderful quick results. More important is the agreement of valid evidence to date that these benefits can be maintained apparently indefinitely.

Unwarranted optimism should be discouraged. Insulin is not a cure of diabetes. Remarkable gains of tolerance credited to insulin are generally explainable by failure to ascertain first the degree of improvement that could be achieved by diet alone. The few instances of genuine recovery of tolerance, beyond what is possible with diet, are best explained by the more thorough rest of the pancreatic function with diet plus insulin than with diet alone. Insulin is not even a magic preventive of progressiveness, for we have seen marked loss of tolerance in patients who were taking considerable quantities of insulin and at the same time excreting much sugar.

On the other hand, it is now fairly certain that diabetes is not an inherently progressive disease. The progressiveness observed in the past has been due chiefly to hydropic degeneration of islands, the result of functional overstrain entailed by incorrect diet and,

* Address before the Mississippi Valley Medical Association, Hot Springs, Ark., October 10, 1923.

to less degree, by occasional injuries from intercurrent infections. I arrived at this conclusion some years ago on the basis of animal experiments, confirmed by experiences with human cases. If this view is not correct, and if there is an inherent progressive element in diabetes apart from functional injury, the outlook is still gloomy, because all cases of the severe or "progressive" type may still be expected to lose tolerance until they finally reach the stage of "total" diabetes and must receive all their insulin from the outside. But the halting of progressiveness is now so much easier with the combination of insulin and diet, and will therefore be witnessed by so many more observers, that the traditional pessimistic view will doubtless soon lose its former dominance unless some real evidence is found to support it. Discarding this unsupported and exploded tradition of inevitable progressiveness, we may say that the most hopeful feature of treatment with a non-curative pancreatic extract is found in the fact that adequate functional relief of the pancreatic islands frequently permits some recovery of assimilative power, and at least suffices under any ordinary conditions to prevent any further impairment of tolerance.

II. Regulation of Total Calories and Body Weight. The announcement of the undernutrition treatment in 1914 attracted attention second only to that centered upon insulin today. The principle was actually revolutionary, for it was a conception that diabetes involves a disorder of total metabolism and a denial of the universal view that it is a disturbance of sugar metabolism alone. The mismanagement of the research and the obstacles which impeded its publication prevented this doctrine from being generally understood or accepted, and, therefore, the treatment itself has lately been attacked or abandoned to a great extent. The discovery of insulin in no way diminishes the importance of this principle. On the contrary, insulin furnishes a new means of demonstrating the validity of this principle and accordingly the nature of diabetes, and this fundamental conception of diabetes furnishes the means for the intelligent regulation of the use of insulin and for preventing dangers or failures.

The undernutrition treatment has meant a reduction of the body weight and metabolism to correspond to the reduced pancreatic island function. We have always agreed with our opponents, who declared that they did not wish their diabetics to be undernourished and weak, but wished them to be plump and strong. The unfortunate fact is, however, that before the discovery of insulin there was no treatment that ever kept severely diabetic patients plump and strong, and, therefore, the only question was what treatment would keep them in the best condition for the longest time. Diabetic patients have emaciated and died, not from lack of food but from lack of the power to assimilate their food. Even the few who have literally been starved to

death have been thus deprived only because they could assimilate scarcely any food if it were given, and their number is infinitesimal compared with those who have needlessly starved to death through the breaking down of their tolerance with quantities of food which they could not assimilate and could only excrete in the urine. I have published elsewhere² the photograph of a young boy as one example out of many to show that undernutrition is not synonymous with starvation. We have not starved patients unnecessarily, and when they have come with mild diabetes we have found that moderate reduction of diet and body weight has saved them from passing into the severe stage. When they were already in a severe stage the choice was unavoidable between reduction of diet sufficient to conserve their tolerance, and a higher diet which would break down their tolerance. We believe that those who have claimed to build up patients by means of diets breaking down the assimilative power, by which alone it is possible to maintain their nutrition, are in a theoretically absurd position, and this belief is confirmed by the significant silence of all such authors concerning their actual statistical results. Furthermore, few seem to have understood the principle which is so important in practice, namely that reduction of weight means raising of tolerance. Therefore, our initial undernutrition for the control of glycosuria and hyperglycemia, which has seemed so radical, has enabled us to give actually higher diets than otherwise possible for cases of this type while keeping symptoms under control. Our published statistics³ show that in the long series of patients faithful to treatment in the Physiatrie Institute, the merest handful have died either from the severity of their diabetes or from infections or other accidents; downward progress in the others has ordinarily been preventable; they have not only survived to receive the benefits of insulin, but in the meantime have been reasonably comfortable and active; they have not reached the extremes of helplessness and misery experienced by those who have tried to avoid undernutrition and ignore active symptoms. The truthfulness of these statistical claims is attested by a sufficient number of witnesses, and these figures, together with those of Joslin⁴ prove that undernutrition has conserved not only life but also strength and comfort more successfully than any other plan of treatment.

The unfortunate feature of every diet treatment has been the emaciation and weakness of all severe cases. Now this is preventable by insulin, but with this new treatment precisely the same problems and disputes are encountered:

1. There are numerous experiments to determine the carbohydrate equivalent of a unit of insulin. The results, which are variable at best, are obtained only under arbitrarily fixed conditions. They may have some value or convenience under the particular conditions chosen, but they have no fundamental sig-

nificance because they vary with the total nutrition and other factors. If insulin is related to the total metabolism it is obviously impossible to establish any fixed general definition of its potency in terms of carbohydrate alone.

2. There is a whole crop of formulas for computing the highest caloric ration that can be given with the minimum of carbohydrate and protein, while avoiding acidosis. These attempts spring from the old idea that only glucose requires consideration in diabetes. It is nothing but a pure theoretical assumption that quantities of carbohydrate, protein and fat which represent supposedly equal quantities of glucose affect the diabetic tolerance equally. This assumption is not only unproved but has been shown by our tests to be untrue.

3. There is the ancient error of mysterious harmful properties in protein, and the much more deep-rooted fallacy of the harmlessness of calories in the form of fat. Low-carbohydrate, low-protein, high-fat diets have been carried to their logical extreme by Petréⁿ, with results which have attracted much notice in Europe but are hopelessly below the standard in this country. Contrary to current suppositions, we have fewer points of difference with Newburgh and Marsh than with many other writers. We agree fully in the endeavor to keep not only the urine but also the blood sugar normal, and in the use of undernutrition not only at the outset but also throughout the course of severe cases. We believe that their clinical success has been due essentially to this use of undernutrition in a series of cases which were distinctly milder than our own series. The use of a high proportion of fat is entirely compatible with restriction of total calories, and is altogether different from absolutely high-fat rations, such as are used in Europe. We must firmly deny, however, that fat in any quantities can be disregarded in its influence on the tolerance, or that fat ever facilitates the clearing up of glycosuria, as compared with fasting or undernutrition. Also, we believe that this or any other return toward the old idea of a disturbance only of glucose metabolism and not of total metabolism in diabetes is a step backward and not forward in both theory and practice.

4. This same consideration applies to all attempts to provide weight or strength for the diabetic by the use of alcohol or of unusual or artificial food materials, such as caramel, odd-carbon fats (intarvin) and so on. These endeavors of chemists must be forever fruitless, because based on a superficial and false conception of diabetes.

For details of experiments showing the influence of total calories and body weight upon diabetes and the insulin requirement, reference must be made to former publications.^{6 7} A few examples are given here:

Table I shows normal urine and blood in a child on a diet of

394 calories. An increase of fat and decrease of carbohydrate, so as to make 804 calories, resulted in hyperglycemia and glycosuria, which ceased when the diet of 394 calories was resumed.

TABLE I.—CASE NO. 574.

Date, 1922.	Diet.				Urine dext., gm.	Plasma sugar, mg. per 100 cc.	Insulin, units, daily.	Body weight, pounds.
	P., gm.	F., gm.	Carb., gm.	Cal.				
Sept. 9 . . .	60	10	16	394	0	...	2	21
10-12 . . .	60	10	16	394	0	...	2	
13 . . .	60	10	16	394	0	100	2	21
14-18 . . .	60	10	16	394	0	...	2	
19 . . .	60	10	16	394	0	126	2	22
20-23 . . .	60	10	16	394	0	...	2	
24 . . .	60	60	6	804	0	...	2	
25 . . .	60	60	6	804	1.7	...	2	20
26 . . .	60	60	6	804	3.7	...	2	
27 . . .	60	60	6	804	8.2	...	2	20
28 . . .	60	60	6	804	3.6	...	2	
29 . . .	60	60	6	804	5.0	...	2	20
30 . . .	60	60	6	804	6.2	...	2	
Oct. 1 . . .	60	60	6	804	8.7	...	2	21
2 . . .	60	60	6	804	10.1	...	2	
3 . . .	60	10	16	394	7.1	254	2	21
4 . . .	60	10	16	394	5.8	...	2	
5 . . .	60	10	16	394	0	...	2	21
6-13 . . .	60	10	16	394	0	...	2	
14 . . .	60	10	16	394	0	159	2	21
15 . . .	60	10	16	394	0	...	2	
16 . . .	60	10	16	394	0	...	2	
17 . . .	60	10	16	394	0	...	2	21
18 . . .	60	10	16	394	0	...	2	
19 . . .	60	10	16	394	0	100	2	21

Another child, Table II, had gradually developed hyperglycemia and glycosuria on a diet of 1400 calories. The replacement of 100 gm. fat by 10 gm. carbohydrate, reducing the calories to 535, resulted in the clearing of these symptoms with the same dosage of 7 units of insulin. With a resumption of the 1400-calorie diet, the insulin requirement was found to be 18 units per day even with hyperglycemia. Thus, the insulin requirement on the higher ration was between two and three times as much as on the lower one.

In Table III there was hyperglycemia without glycosuria on 346 calories and 6 units of insulin daily. The fat intake was increased by 150 gm. without changing the protein or carbohydrate, and the resulting glycosuria was controlled only by an increase of insulin to 32 units daily. This increased requirement is out of all proportion to any glucose content attributed to the fat under any theories now prevalent in this country.

TABLE II.—CASE NO. 989.

Date, 1922.	Diet.				Urine dext., gm.	Plasma sugar, mg. per 100 cc.		Insulin, units daily.	Body weight, pounds.
	P., gm.	F., gm.	Carb., gm.	Cal.		7 A.M.	8 P.M.		
Sept. 1 . . .	60	115	30	1400	...	312	..	7	
2 . . .	60	115	30	1400	Faint	200	..	7	36
3 . . .	60	115	30	1400	0	7	
4 . . .	60	115	30	1400	6.0	306	334	7	36
5 . . .	60	15	40	535	5.3	306	..	7	
6 . . .	60	15	40	535	1.9	..	366	7	36
7 . . .	60	15	40	535	3.3	283	..	7	
8 . . .	60	15	40	535	4.0	..	283	7	36
9 . . .	60	15	40	535	4.8	250	..	7	
10 . . .	60	15	40	535	4.8	7	36
11 . . .	60	15	40	535	0	195	223	7	
12 . . .	60	15	40	535	0	7	36
13 . . .	60	15	40	535	0	157	..	7	
14 . . .	60	15	40	535	0	7	36
15 . . .	60	15	40	535	0	7	
16 . . .	60	15	40	535	0	203	..	7	36
17-18 . . .	60	15	40	535	0	7	
19 . . .	60	15	40	535	0	126	..	7	36
20 . . .	60	15	40	535	0	..	300	7	
21 . . .	60	15	40	535	0	139	..	7	36
22-23 . . .	60	15	40	535	0	9	
24 . . .	60	15	40	535	0	137	260	9	36
25 . . .	60	115	30	1400	0	9	
26 . . .	60	115	30	1400	0	9	36
27 . . .	60	115	30	1400	0	..	270	6	
28 . . .	60	115	30	1400	1.4	226	..	10	36
29 . . .	60	115	30	1400	Faint	12	36
30 . . .	60	115	30	1400	Faint	..	200	14	
Oct. 1 . . .	60	115	30	1400	Faint	16	36
2 . . .	60	115	30	1400	0	16	
3 . . .	60	115	30	1400	0	18	36
4 . . .	60	115	30	1400	0	164	..	18	
5 . . .	60	115	30	1400	0	18	37
6 . . .	60	115	30	1400	0	18	
7 . . .	60	115	30	1400	0	18	37

In Table IV, as in the preceding ones, the plasma sugar figures are those obtained mornings before breakfast. This patient, on his diet of 40 gm. protein, 10 gm. carbohydrate and 380 calories, began to develop hypoglycemic attacks in the evenings. The attempt was made to control these by increasing the protein to 100 gm. and 200 gm., but they continued until the protein was raised to 300 gm. Here the insulin was increased to 9 units daily, but this extra requirement could readily be accounted for by the simple increase of calories. To test this possibility the protein was sharply reduced to 90 gm. on December 22. The calories were kept the same, but the theoretical glucose value of the new

TABLE III.—CASE NO. 1073.

Date, 1922, 1923.	Diet.				Glyco- suria, gm.	Plasma sugar, mg. per 100 cc.	Insulin, units daily.	Body weight, pounds.
	P., gm.	F., gm.	Carb., gm.	Cal.				
Nov. 11 . . .	40	10	24	346	0	...	4	112
12 . . .	40	10	24	246	0	...	6	111
14 . . .	40	10	24	346	0	195	6	110
16 . . .	40	10	24	346	0	156	6	112
17 . . .	40	10	24	346	0	182	6	...
19 . . .	40	160	24	1696	0	195	6	111
23 . . .	40	160	24	1696	++	312	6	112
Dec. 1 . . .	40	160	24	1696	++	326	6	113
10 . . .	40	160	24	1696	57.83	349	6	113
12 . . .	40	160	24	1696	18.64	...	10	113
14 . . .	40	160	24	1696	36.21	405	10	113
17 . . .	40	160	24	1696	20.25	...	14	...
21 . . .	40	160	24	1696	37.59	...	14	114
23 . . .	40	160	24	1696	15.37	...	18	...
27 . . .	40	160	24	1696	4.76	349	18	116
Jan. 4 . . .	40	160	24	1696	10.69	...	20	118
5 . . .	40	160	24	1696	8.93	306	20	116
7 . . .	40	160	24	1696	11.00	349	22	116
10 . . .	40	160	24	1696	20.49	...	24	...
11 . . .	40	160	24	1696	18.80	385	24	116
14 . . .	40	160	24	1696	5.77	...	28	...
16 . . .	40	160	24	1696	+	319	28	119
17 . . .	40	160	24	1696	0	246	28	120
18 . . .	40	160	24	1696	0	238	32	...
19 . . .	40	160	24	1696	0	...	32	120
21 . . .	40	160	24	1696	0	200	32	...
23 . . .	40	160	24	1696	0	206	32	...

TABLE IV.—CASE NO. 1274.

Date, 1922, 1923.	Diet.				Glyco- suria, gm.	Plasma sugar, mg. per 100 cc.	Insulin, units daily.	Body weight, pounds.
	P., gm.	F., gm.	Carb., gm.	Cal.				
Nov. 23 . . .	25	10	10	230	0	366	6	105
26 . . .	25	10	10	230	0	234	6	105
29 . . .	25	10	10	230	0	185	6	107
30 . . .	40	20	10	380	0	...	6	109
Dec. 2 . . .	40	20	10	380	0	112	6	111
3 . . .	80	25	10	585	0	125	6	111
4 . . .	80	25	10	585	0	102	6	114
6 . . .	100	25	10	665	0	...	6	116
7 . . .	100	25	10	665	0	62	6	116
9 . . .	200	25	10	1065	0	87	6	115
10 . . .	200	25	10	1065	0	112	6	109
11 . . .	200	25	10	1065	0	175	6	...
12 . . .	300	25	10	1465	0	203	6	111
14 . . .	300	25	10	1465	0	230	6	113
15 . . .	300	25	10	1465	0	238	9	...
18 . . .	300	25	10	1465	0	92	9	114
19 . . .	300	25	10	1465	0	175	6	...
22 . . .	90	111	25	1465	0	209	9	112
28 . . .	90	111	25	1465	0	178	9	111
29 . . .	90	111	25	1465	0	209	9	...
Jan. 1 . . .	90	111	25	1465	0	168	9	106
3 . . .	90	111	25	1465	0	...	9	106

diet was much lower than of the former one. The insulin requirement was not particularly changed. Protein, therefore, not only has no extraordinary glycosuric effect because of specific dynamic or any unknown influence, but actually shows less effect than anticipated from its theoretical glucose content.

TABLE V.—CASE NO. 85.

Date, 1923.	Diet.				Urine.		Plasma sugar, mg. per 100 cc.*	Insulin, units daily.	Body weight, pounds.*
	P., gm.	F., gm.	Carb., gm.	Cal.	Sugar, gm.*	T.N., gm.*			
Mar. 11-17	60	151	100	2000	Tr.	..	350	40	109
18-31	60	262	100	3000	0	..	249	40	113
April 1- 3	60	362	90	3860	0	..	160	40	114
4-11	60	362	90	3860	9.8	..	303	30	116
12-30	60	362	90	3860	0	..	268	33	120
May 1- 5	60	362	90	3860	15.0	..	397	33	125
6- 8	60	362	90	3860	17.1	..	469	36	125
9-10	60	362	90	3860	21.1	..	652	40	125
11-12	60	362	90	3860	25.7	44	125
13-15	60	362	90	3860	22.6	..	416	48	126
16-17	60	362	90	3860	22.0	52	128
18-19	60	362	90	3860	26.8	3.7	429	54	129
20-22	60	362	90	3860	38.5	5.3	...	60	130
23-26	60	362	90	3860	40.4	6.9	455	66	130
27-31	60	362	90	3860	19.2	6.1	357	75	131
June 1- 2	60	362	90	3860	28.1	6.9	326	80	133
3- 9	160	317	90	3860	60.3	13.1	437	80	135
10-13	160	317	90	3860	33.7	16.5	500	90	137
14-19	60	336	148	3860	45.3	8.3	441	90	139
20-26	60	336	148	3860	42.3	5.7	429	100	141
27-30	60	336	148	3860	74.5	6.2	484	120	143
July 1- 7	60	336	148	3860	42.9	5.8	600	120	144
8-14	60	336	148	3860	20.5	5.6	422	140	147
15-18	60	336	148	3860	23.9	5.7	357	140	149
19-Aug. 4	160	317	90	3860	45.2	17.5	443	140	153
5-19	60	336	148	3860	71.5	7.9	455	140	159
20-29	60	136	148	2060	43.4	7.1	410	140	160
30-Sept. 4	60	157	100	2060	13.8	7.4	366	140	159
5-20	60	180	50	2060	8.5	8.1	381	120	158
21-24	60	80	60	1200	5.6	9.7	295	90	155
25-30	60	80	60	1200	6.5	9.5	258	80	154
Oct. 1- 2	60	80	60	1200	4.7	13.4	300	80	153
3	60	80	60	1200	4.7	12.9	...	70	152

* Average.

Table V represents a prolonged experiment which is still in progress. The patient is a young physician with the severe "progressive" type of diabetes, whose tolerance has been accurately known and undiminished during the past four years. On the first diet of 2000 calories his insulin requirement was 40 units. An increase of fat to make 3000 calories apparently produced no change from March 18 to 31, so that from an experiment of this duration the

fat might be regarded as harmless. In April 100 gm. more of fat was added, and 10 gm. carbohydrate was subtracted to allow for the theoretical glycerol of the fat. The first result was that the insulin dosage had to be reduced to 30 units daily to prevent evening hypoglycemic attacks, because the immediate effect of the carbohydrate withdrawal was so much greater than that of the fat addition. With the gradual increase of body weight came heavy glycosuria, in spite of a doubling of the original insulin dosage. An increase of protein from 60 to 160 gm. daily made no important difference. On June 14 the extra protein was replaced by its theoretical equivalent of carbohydrate, keeping the total calories unchanged, and the glycosuria rose and persisted notwithstanding an increase of insulin to 140 units daily. By a repetition of these changes in August, the more powerful glycosuric influence of carbohydrate, as compared with protein, was confirmed. Nevertheless, the effect of the total calories was dominant. August 20 to 29 the glycosuria fell to an average of 43.4 gm., as compared with 71.5 gm. in the preceding period, because of the subtraction of 200 gm. of fat without change in the protein or carbohydrate. In order to save time a general reduction of diet has since been made, and with the reduction of body weight the insulin requirement has been reduced to 70 units. This experiment, which altogether will cover nearly a year of continuous hospital observation, will be published in greater detail when it is finished, but from the results of numerous other experiments I have no hesitation in predicting the outcome. We shall not reduce the weight to the original low level, but in proportion as we reduce it we shall reduce the insulin requirement. With a low body weight and low total calories we shall be able to give 148 gm. carbohydrate or 160 gm. of protein per day without creating a requirement for anything like 140 units of insulin per day.

As yet nothing is known of the physiological-chemical role of insulin; whether it enters directly into the metabolism of all foods, or whether it is directly related only to glucose and other foods merely modify the utilization of glucose. As shown elsewhere,⁸ it is obvious that in brief experiments the glycosuric effect of carbohydrate is greatest, of protein is intermediate and of fat is least. We are still uncertain whether these differences will hold good after one or two years, or whether after a sufficiently long period the insulin requirement for a certain number of calories may be practically identical, irrespective of the kinds of food furnishing the calories. The chief point to emphasize is that the influence of fat is slow, but it gradually produces the traditional appearance of "spontaneous downward progress," so that more and more insulin is required to control glycosuria. With excessive fat rations a condition is finally reached when the abnormally fattened patient can scarcely be kept free from glycosuria by any quantities of

insulin that can be poured into him. Relief is to be found not in restriction to minimal quantities of protein and carbohydrate, but in suitable regulation of total calories and body weight. We shall still give most of the calories in the form of fat, because the sudden ups and downs of blood sugar resulting from excessive carbohydrate or protein are thus avoided. But in average cases comfort, strength and convenience are served by allowing in the neighborhood of 100 gm. carbohydrate and 100 gm. protein daily, and any excessive insulin requirement is avoided by restriction of fat and total calories so as to keep the body weight perhaps 5 or 10 pounds below the full normal.

III. Dangers from Incorrect Diets. Glycosuria and hyperglycemia are abnormalities. They can be prevented, especially in severe cases, only by carefully weighed diets and equally exact regulation of insulin dosage. These precautions are inconvenient for both physician and patient, but it is a question whether there can be any plan of using insulin which will make a combination of careless diet and sugar excess permanently safe.

Theorizing on this subject is not warranted. Granting that sufficient insulin dosage will for the time being keep a patient in apparent health regardless of more or less glycosuria, it is still necessary to consider the long-familiar dangers of diabetes, which may be classified chiefly as: (a) Infections, (b) vascular and organic changes and (c) acidosis.

(a) Past experience with infections has established two facts: (1) Hyperglycemia and glycosuria create an abnormal susceptibility to all kinds of infections; they occur not only in severe cases but also in mild ones, in patients whose pancreatic function has enabled them to be both strong and obese for years without regard to diet or glycosuria. (2) Our very severe cases, kept in a state of emaciation with normal blood sugar, have shown a remarkable immunity to infections and have healed their wounds perfectly after operations. Liability to infections, therefore, seems to be not governed by the insulin supply or state of apparent nutrition, but to be connected strictly with the presence of excess sugar.

(b) Arteriosclerosis is probably demonstrable in every case past middle-age in which glycosuria has been present for ten years or more. Gangrene generally has a basis of arteriosclerosis, but there is a specific nutritive factor besides, shown by the usual response to treatment which reduces the sugar. Retinitis, cataract, neuritis and deteriorations in many organs may be attributed either to circulatory trouble or to the direct nutritive abnormality. These disturbances also are not connected with the available quantity of insulin or the apparent nutritive state, for they are practically as frequent in mild as in severe cases, and they are halted or prevented by undernutrition, however extreme, which controls the sugar.

(c) Diabetics who are fattened by the aid of large doses of insulin seem to become peculiarly subject to acidosis from slight causes. Theorists may suppose that a certain insulin dosage will metabolize enough carbohydrate to prevent acidosis under any circumstances, but the fact is that with a tendency to acidosis insulin diminishes remarkably in its effectiveness and much larger doses are required, as shown in the treatment of coma.

We have endeavored to keep our patients strictly free from glycosuria and with plasma sugar as nearly normal as possible. This attempt has succeeded in the vast majority of cases, but a few patients have been careless or disobedient. There is already a plain difference between the two groups, which seems more than accidental. The sugar-free group has remained free from all accidents, except a few trivial colds which have passed off uneventfully. Practically the entire group with glycosuria and marked hyperglycemia are now included in the following list of deaths and complications, classified under the same three heads as above. The earlier details of most of these cases are given in our former publication.¹

CASE I.—No. 1047. Girl, aged three years; at home on a diet of 55 gm. protein, 50 gm. carbohydrate and 1000 calories, with 10 to 14 units of insulin daily. The case was severe, and glycosuria and hyperglycemia were frequent despite the parents' efforts. There was a middle-ear abscess, and the diet was reduced to 50 gm. protein, 35 gm. carbohydrate and 900 calories. The child is still rather fat at a weight of 34 pounds, and her sugar is controlled better but not perfectly. She has recently come safely through whooping-cough.

CASE II.—No. 1372. Woman, aged fifty-seven years, was admitted, April 15, 1923, with diabetes diagnosed a year previously. She had had frequent boils, besides other symptoms. She was discharged, May 5, symptom-free on 75 gm. protein, 70 gm. carbohydrate and 2000 calories, without insulin. By slight carelessness she allowed glycosuria to return early in July, and during that month developed an infection of a finger with severe cellulitis of the hand, requiring multiple incisions and drainage. The condition was again controlled without insulin.

CASE III.—No. 3. Girl, aged fifteen years, was first treated in 1915, and was free from important infections during undernutrition treatment since that time. With a height of 5 feet 3½ inches, she increased her weight by means of insulin from the former 80 pounds to 130 pounds. At this weight, with a diet of 100 gm. protein, 100 gm. carbohydrate and 3000 calories, she was taking 100 units of insulin per day and showing glycosuria most of the time.

She developed at intervals an abscess from an insulin injection, a middle-ear infection and a severe tonsillitis. The attempt has been made to reduce her diet, weight and insulin dosage, but she is inclined to be careless.

CASE IV.—No. 806. Girl, aged nine years, who had developed severe diabetes at seven years. In 1923 she was treated with insulin, and up to August was sugar-free and in excellent health on 50 gm. protein, 50 gm. carbohydrate and 1000 calories, with 36 units of insulin per day. She was not seen after that time, as the mother became discouraged with the tendency to evening hypoglycemia when the child was sugar-free, and found she could more conveniently be kept in apparent health by allowing glycosuria every morning, which was cleared up by the insulin given during the day. In September she had a severe middle-ear infection requiring paracentesis and attended by increased glycosuria. A few days later a long-distance telephone message from the mother described symptoms of impending coma, and she was advised to continue the same insulin and omit all food except carbohydrate. The coma symptoms disappeared within twenty-four hours, but the other ear became involved, and later there was a patch of infection in one lung. The fever was above 105° , and the family physician considered removal to an institution unsafe. The infection seems finally to have been overcome, but the diabetes is not yet under control.

CASE V.—No. 1559. Woman, aged fifty-nine years, with diabetes diagnosed in 1908, and with loss of parts of several toes in successive attacks of gangrene since that time. With a height of 5 feet 6 inches, her weight was 245 pounds at onset and 170 pounds at admission, August 22, 1923. Her weight was then further reduced by a diet of 80 gm. protein, 40 gm. carbohydrate and 600 calories. With 15 units of insulin per day she was constantly free from glycosuria, but had plasma sugar always above 0.25 per cent. After a month in this condition blisters developed simultaneously at the ends of both great toes. The insulin was immediately increased to 27 units in order to reduce the hyperglycemia. One toe is healing but the other shows a superficial black area with a prognosis still in doubt.

CASE VI.—No. 1576. Woman, aged fifty-six years. January, 1923: Height, 5 feet 4 inches; weight, 190 pounds. Diabetes was diagnosed after she had lost 30 pounds in the following six months. She was admitted, September 9, 1923, because of a swelling like an infected bunion on the right foot. On a diet of 60 gm. protein, 35 gm. carbohydrate and 600 to 700 calories she was free from glycosuria and the infection gradually subsided. The plasma sugar was

never found below 0.24 per cent, and recently the left great toe became red and blistered. Insulin was immediately increased from 20 to 27 units to reduce the hyperglycemia, and the toe is now healing rapidly.

These two cases are noteworthy as being the only ones in the history of the Institute in which anything like gangrene developed during the period of hospital care. It is also noticeable that they were being treated with both undernutrition and fair quantities of insulin, and were free from glycosuria. Before the discovery of insulin we controlled hyperglycemia more strictly by more radical undernutrition, and these cases seem to show that carelessness regarding hyperglycemia is still not safe.

CASE VII.—No. 989 was described at length¹ as an example of a girl, aged eight years, who was fattened beyond our usual custom, because of the safety afforded by the constant care of a skilled nurse. On a diet of 80 gm. protein, 125 gm. carbohydrate and 2000 calories, she was almost constantly free from glycosuria for several months with 70 units of insulin daily. Glycosuria was then present for only two days, when the nurse telephoned a description of symptoms which were interpreted as hypoglycemia. As glycosuria at one time of day is compatible with hypoglycemia at another time, it was proposed for this attack to give added carbohydrate and omit an insulin dose. The finding of both heavy sugar and acetone in the urine, however, showed that the condition was actually the atypical form of impending coma which is so frequent in such cases. A blood test showing high plasma sugar and acetone and low bicarbonate confirmed the diagnosis, and increase of insulin and a diet of pure carbohydrate cleared up everything promptly. Later it gradually became necessary to increase the insulin to 106 units daily to prevent glycosuria, at a weight of 65 pounds. Therefore the diet was reduced to 1500 calories without changing the protein or carbohydrate, and with a reduction of 3 or 4 pounds of weight the insulin requirement has again been brought down between 60 and 70 units per day.

CASE VIII.—No. 1341. Girl, aged six years, was diabetic since February, 1923. She was symptom-free on a diet of 50 gm. protein, 42 gm. carbohydrate and 840 calories, with only 4 units of insulin per day. The mother became careless, did not bring the child for tests, allowed glycosuria to develop and finally brought her back in coma on September 18. The coma required the administration of 185 units of insulin in the first twenty-four hours, and a permanent increase of dosage to 30 units per day has since been necessary.

CASE IX.—No. 1350. Girl, aged fifteen years; height, 5 feet 8 inches; weight, 106 pounds. She was discharged symptom-free, March 29, 1923, on 80 gm. protein, 80 gm. carbohydrate and 1800 calories, with 8 units of insulin per day. The parents continued the treatment, but failed to prevent repeated violations of diet and never brought the child for tests. She died in coma, September 1.

CASE X.—No. 229. Girl, aged eight years, severely diabetic since 1920, was kept alive by intermittent undernutrition with departure from diet between. Her height was 3 feet 7 inches and her weight 41½ pounds. In April, 1923, she weighed 55½ pounds on a diet of 70 gm. protein, 75 gm. carbohydrate and 1900 calories, with 36 units of insulin per day. The parents were never careful in keeping her strictly sugar-free, as she looked the picture of health, and they trusted the insulin to keep her safe. Heavy glycosuria was known to be present for a week or two at the end of June, and they planned to bring the child to the Institute within a few days when their vacation in Atlantic City was finished. She suddenly became unwell, and before the parents realized what was wrong was in deep coma. Death occurred thus on July 3 notwithstanding treatment with 250 units of insulin.

These cases show an extremely high proportion of dangerous or fatal accidents, with either low or high insulin dosage, with heavy glycosuria, slight glycosuria or sometimes only marked hyperglycemia. Our experience, therefore, is in favor of maintaining the closest possible approximation of normal conditions by rigid accuracy of diet and insulin dosage. Institutional care is as much needed as ever for the thorough study of cases and instruction of patients.

All questions involved in the diet and the entire management must be settled by unbiased objective tests. Nobody in the world can decide anything by a mere expression of opinion for or against undernutrition or any other procedure. The whole literature of diabetes is inexcusably befogged with statements of mere impressions by supposed authorities, accompanied by garbled accounts of brief observations which appear to support their position, without any following-up of these cases with subsequent reports of fatalities or other embarrassing events. We have reached a stage of metabolic study where definite proof is possible. Indefinite dicta are as much out of date as it would be for somebody to arise and remark ponderously, without any specific facts, that "From his wide clinical experience he is convinced that typhoid fever is not caused by the *Bacillus typhosus*." The problems of a chronic disease require observations not only sufficiently exact but also sufficiently prolonged. They can be illuminated if everyone will record his experience fully and frankly, without regard to the

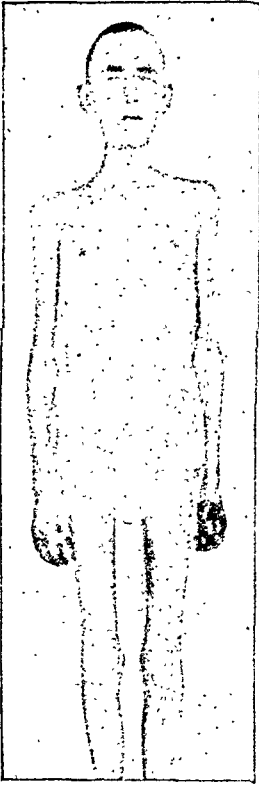


FIG. 1



FIG. 2

FIGS. 1 and 2.—Case 823. Age, twenty-seven years. October 28, 1922. Before insulin.

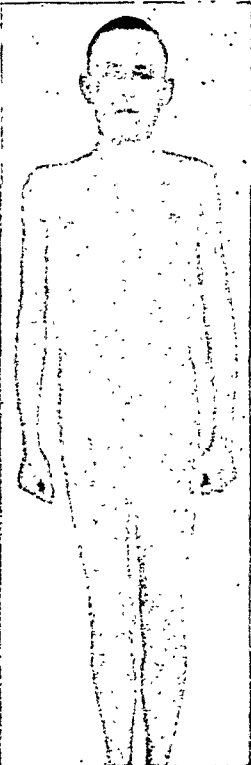


FIG. 3



FIG. 4

FIGS. 3 and 4.—Case 823. April 10, 1923. After insulin.

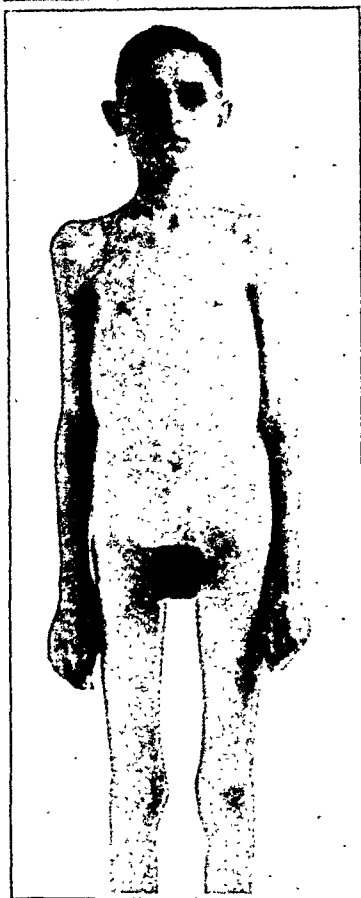


FIG. 5

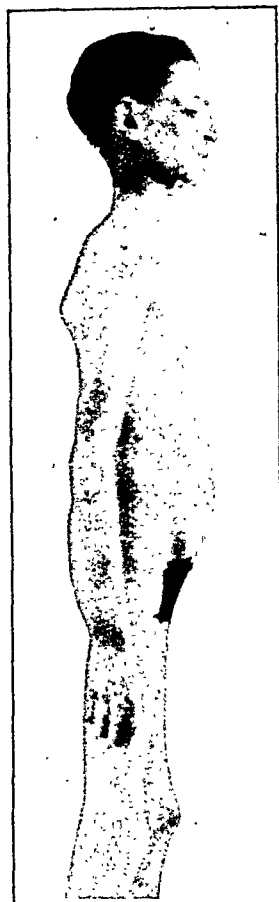


FIG. 6

FIGS. 5 and 6.—Case 916. Age, eighteen years. February 25, 1923. Before insulin.

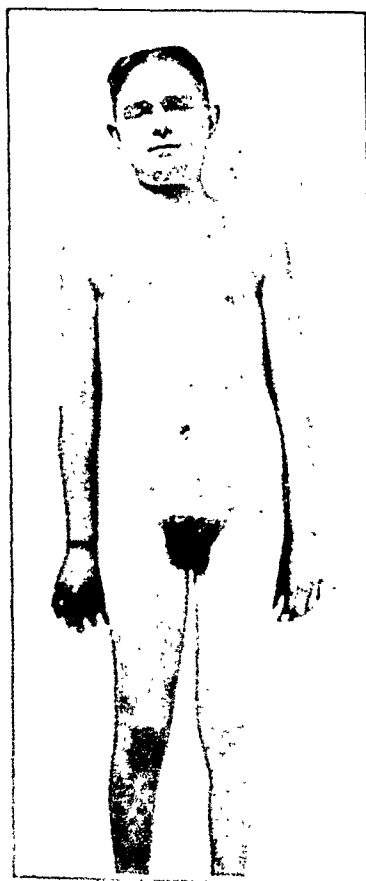


FIG. 7

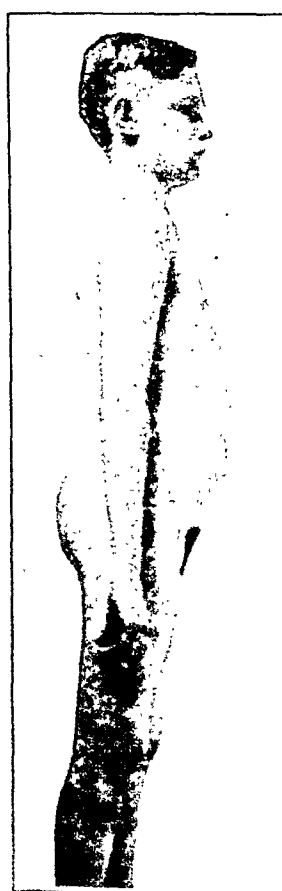


FIG. 8

FIGS. 7 and 8.—Case 916, Oct. 10, 1923. After insulin. The patient was made slightly obese. Pictures show abnormal appearance resulting, somewhat suggesting adiposa genitalis. Diet and weight have since been reduced to a normal scale.

effect upon himself or his previously expressed opinions. It is to be feared that the advocates of lax methods will not hold themselves to that strict standard. It is still more to be feared that a widespread misunderstanding and misuse of insulin will cause the initial benefits to be only temporary, so that the diabetic death-rate, which seems already to have fallen, will later rise. This has been the history with undernutrition and with every other advance in treatment; the patients have not died so early, but they have died nevertheless. The same old dangers of acidosis and infection still exist, and they can be met only by the same rigid care in keeping diabetes under control. The essential difference introduced by insulin is that this result can be accomplished at a higher level of nutrition, and there is the further hope that a greater number of physicians will now be stimulated to learn and apply exact methods for the settlement of theoretical questions and for the practical care of patients.

Conclusion. The practical point which I have emphasized is the importance of total calories and body weight in relation to diabetic tolerance and the insulin requirement. Increase of weight requires more insulin. Reduction of total diet and weight makes possible the complete control of symptoms without serious privations in carbohydrate or protein or excessive use of insulin. In our experience patients with glycosuria or marked hyperglycemia are subject to various dangerous complications regardless of low or high insulin dosage. The treatment of diabetes has been improved but not simplified by insulin, and neglect of strict dietary care should be condemned.

REFERENCES.

1. Jour. Metab. Res., 1922, 2, 547.
2. Allen, F. M.: Nelson's Loose Leaf Medicine, 1920, 3, 90.
3. Allen, F. M., and Sherrill, J. W.: Jour. Metab. Res., 1922, 1, 377.
4. Joslin, E. P.: Treatment of Diabetes Mellitus, 1917.
5. Petré, K.: Diabetes-Studier, Copenhagen, 1923.
6. Allen, F. M.: Jour. Metab. Res., 1923, 3, 61.
7. Allen, F. M.: Tr. Assn. Am. Phys., 1923, 38, 394.
8. Sherrill, J. W.: Jour. Metab. Res., 1923, 3, 13.

THE USE OF INSULIN IN TREATMENT OF DIABETES. REPORT OF SOME CASES.

By W. E. NICELY, M.D.,

AND

C. C. EDMONDSON, M.D.,

WAUKESHA, WIS.

INSULIN is not given to all cases of diabetes indiscriminately, nor to all patients who wish to take it. It has seemed advisable to limit its use to selected types of cases. The immediate welfare of the

patient, his future mode of living, his economic status, his occupation, are all taken into consideration, as well as the severity of his diabetes. Accordingly we have given insulin to the following patients:

1. Those who are unable to keep diabetes under control on diets of at least 1600 to 1800 calories daily, or, in other words, who are unable to maintain metabolic balance, and who must remain at light work, at least.

2. Those who are acutely ill, in threatened or actual coma.

3. Those who have gangrene, local or general infections, or complications requiring surgical treatment.

4. Those who have diabetes complicated by chronic nephritis, in order to make possible a greater carbohydrate intake, and maintain metabolic balance with a minimum protein intake, and to use the fruit juices more freely.

5. Children.

The following 6 cases of diabetes are presented in detail, as illustrating some of the types above mentioned. These were treated in the early part of our experience with insulin, and were handled with possibly more caution than some of the later cases, when we had learned more of the possibilities of the new remedy. In our treatment, it is fair to mention that due to the expense of sanitarium treatment, and the consequent short, or relatively short, period of time that patients are under direct care, it is often necessary to proceed with probably a little more haste than if the patients were from this community and were under observation for an indefinite period of time.

CASE I.—J. B. P., male, aged thirty-seven years, first came to us for treatment in June, 1920, with history of only six weeks' duration of polyuria, thirst, and loss of weight, with sugar having been found in the urine only six days prior to entering the sanitarium. Physical examination then showed a healthy looking man, with enlarged thyroid, slight exophthalmos, slight degree of pyorrhea, rapid pulse, heart not appreciably enlarged, pounding vigorously, with a systolic murmur at apex only, a left inguinal hernia well held by a truss, and a left hydrocele. The weight was 163 pounds. The urine contained 1 per cent of sugar and a marked amount of diacetic acid. The blood sugar was 0.25 per cent. A diet of about 1100 calories, 60 gm. protein, 88 gm. fat, and 18 gm. carbohydrate, eliminated the sugar and diacetic acid from the urine in three days, and reduced the blood sugar to 0.167 per cent in four days. The diet was gradually increased to about 2150 calories, with 82 gm. of protein, 164 gm. fat, and 86 gm. of carbohydrate. The urine remained sugar-free for the remaining four weeks under observation, and the blood sugar did not go above 0.133 per cent. The tachycardia subsided somewhat with thorough rest.

CASE I.*—AGED FORTY YEARS: WEIGHT 142 POUNDS.

Date.	Urine sugar, gm.	Urine, diabetic acid.	Blood sugar, per cent.	Insulin, units.			Diet.			
				B.	D.	S.	C.	P.	F.	Cals.
Nov. 8	40.0	0.250	25	64	83	1100
9	43.2									
10	21.3	++								
11	22.2	+++								
12	25.0	+								
13	15.8	++	4	37	22	360
14	16.3	++++	0.208							
19	11.0	++++	0.198							
25	14.0	++	0.200							
29	9.6	○	0.181							
Dec. 1	14.4	++								
5	28.4	+	0.200							
11	14.4	+	0.184							
13	18.0	○								
15	10.7	tr.	0.206	..	2	2	13	26	66	750
17	3.9	tr.	3	3				
18	7.6	tr.	3	3				
19	tr.	○	0.166	..	3	4	18	40	85	1000
20	sl. tr.	○	4	4				
22	0	+	0.143	..	4	4				
26	0	○	0.154	..	4	5				
30	0	○	0.158	..	5	5				
Jan. 4	0	○	0.130	5	5	5	Same as before.			
9	0	○	0.114	5	5	5	28	42	103	1200
13	0	○	0.143	5	5	5				
18	0	○	0.129	5	5	5				
23	0	○	0.131	5	5	5				
27	0	○	0.113	5	5	5				
Feb. 1	0	○	0.106	5	5	5				
2	0	○	..	8	8	8	44	63	122	1525
6	0	○	0.112							
7	0	○	..	10	10	10				
8	0	○	..	10	10	10	53	77	132	1700
12	0	○	0.115	10	10	10				
15	0	○	..	10	10	10	78	80	157	2045
17	0	○	0.129	10	10	10				
22	0	○	0.108	10	10	10				
27	0	○	0.125	10	10	10	78	80	157	2045

The urine continued sugar-free on daily testing.

Left sanitarium, February 27.

* Daily estimations of sugar elimination and ketones were made in all cases, but in order to abbreviate tables only results are recorded on days on which blood-sugar estimations were made or treatment modified.

On November 8, 1922, he returned. He had lost about 20 pounds in weight. He was beginning to feel weak. Sugar had been present in the urine for several months. Diet reduction had failed to clear it up. Physical examination showed the goiter much reduced in size, the heart beating vigorously, but with no murmur, and rate about 80; pyorrhea more advanced, with marked retraction of the gums and gingivitis; some loss of weight. The urine contained about 2 per cent of sugar and the blood again 0.25 per cent. This time diet regulation was not so successful as two years before. The diet was even reduced to very low values without success in clearing the urine of sugar, or bringing the blood sugar down but a small amount.

On December 15 insulin was begun. At once the feeling of weakness and hunger disappeared, and was replaced by a feeling of well-being. The course of the urine and blood sugar, the diet, the insulin dosage, are shown on the chart. After the diabetes was thoroughly under control, two teeth that were shown by roentgen-ray to have apical infection, were extracted, without any subsequent disturbance of the blood sugar.

He went home with urine sugar-free, containing no diacetic acid nor acetone, and with the blood sugar about normal. He has continued to administer the insulin to himself, 10 units before each meal, and has maintained control of his diabetes until the present time. The last report from him and urine analysis showed a trace of sugar. A slight change of diet was advised, which will probably result in the elimination of even the trace of sugar. He has felt perfectly well, and has worked six hours a day, as a bank cashier. He has confidence in himself and is hopeful for the future.

CASE II.—T. F., male, aged twenty-five years, came to the sanitarium with the history of having sugar found in the urine two days prior to entrance. He had suffered with excessive thirst for four weeks, and had excessive appetite for two weeks before the urine was tested. Nineteen months before he had passed an examination for life insurance.

When first seen by us, he was evidently quite sick, very weak, very drowsy and listless, with breathing slightly increased in rate and depth, with mouth and throat dry, red, glazed and the tongue coated, red, and dry. He was very thirsty, drinking a gallon or more of water a day. Further physical examination was negative, except moderately advanced gingivitis type of pyorrhea of the lower incisors, with slight degree of the same about other teeth. The urine contained 2 per cent of sugar and a large amount of diacetic acid. Diet reduction and the administration of a mixture of mono- and disodium phosphates by mouth, eliminated the diacetic acid within twenty-four hours, but the blood sugar declined only very little. Then insulin was given, 5 units three times a day. The urine was sugar-free within twenty-four hours, the blood sugar became normal in a few days. The diet was gradually increased, and after a time the amount of insulin could be decreased. This case shows the value of insulin in early cases of diabetes, acutely sick, in sparing pancreatic function by taking some of the load from the patient's own pancreas, and allowing the weakened function to recuperate. Many times these cases will be found, when the acute symptoms have subsided, to be relatively mild diabetes. This patient went home, obtained light work, and has gotten along well, keeping the blood sugar nearly normal, except after a severe cold, which upset his tolerance somewhat and elevated the blood sugar. He should come in again for adjustment of diet and insulin dosage to the status

of his disease since the cold. Colds seem to have a particularly bad effect on the diabetic's tolerance, and should be treated with great care. We advise patients to go to bed when suffering with a cold, to keep warm, to secure thorough elimination in every way, and to eat less for the time. It is often necessary to readjust diet, or diet and insulin dosage, after a patient has suffered from even a mild cold.

CASE II.—AGED TWENTY-FIVE YEARS: WEIGHT 136 POUNDS.

Date.	Urine sugar, gm.	Urine, diacetic acid.	Blood sugar, per cent.	Insulin, units.			Diet.			
				B.	D.	S.	C.	P.	F.	Cals.
Feb. 13	64.0	++++	0.190							
15	36.2	○								
19	18.0	○	0.173							
20	12.0	○	5	14	39	57	640
21	1.0	○	..	5	5	5				
24	0	○	0.097	5	5	5	24	68	106	1315
25	0	○	..	5	5	5				
Mar. 1	0	○	0.096	5	5	5	48	93	128	1710
6	0	○	0.101	5	5	5	64	102	154	2050
15	0	○	0.094	5	5	5				
16	0	○	5	5				
19	0	○	0.090	..	5					
24	0	○	0.070	..	5	..	64	102	154	2050
Left sanitarium, March 24.										
April 6	Blood test only		0.120							
10	"	"	0.064							
May 19	"	"	0.140							
June 11	"	"	0.188							
25	"	"	0.185							

CASE III.—L. B., male, aged twelve years, came to the sanitarium with the history of having sugar found in the urine only one day before. About a year before, he had been circumcised under ether anesthesia, and a trace of sugar had been found in the urine in one test, but had never been found after that until the diagnosis of diabetes was made. Thirst and excessive frequency of urination had begun three weeks before diagnosis, though he had had difficulty in retaining the urine for four or five years. When first seen by us, he was very drowsy and weak, apparently in beginning coma. Physical examination gave no notable abnormalities, other than his weak condition. The urine contained 8 per cent of sugar, 0.1 per cent of albumin, a very large amount of diacetic acid, and very many hyaline and granular casts. The blood sugar was 0.312 per cent. Ten units of insulin were given at night, and beginning with 6 units the next morning, a 10-unit dose was given every three hours until the urine was sugar-free. The urine was tested every time voided. Abundant fluid was given by mouth. He was kept warm in bed. The diet was kept low, about 18 gm. protein, 18 gm. fat, and 24 gm. carbohydrate. In all, 56 units of insulin were given in the first twenty-four hours. This amount was sufficient to bring the boy

out of beginning coma and free the urine from sugar and diacetic acid. The albumin disappeared from the urine coincidentally with the sugar, and neither albumin nor casts were found thereafter. After the first day, 18 units of insulin, 6 units three times a day, were enough to keep the blood sugar normal and the urine sugar-free. His diet was raised to 103 gm. carbohydrate, 95 gm. protein, 147 gm. fat, 2115 calories. He gained much in strength and some in weight. Although the parents were instructed in the use of insulin and in diet regulation, they never seemed to grasp the idea that the boy needed as much care at home as when in the sanitarium. So after a few days at home they became careless, and omitted the insulin. We learned later that the boy died about a month after leaving our institution. With more intelligent coöperation on the part of the boy's parents, his life might have been spared for a considerable time.

CASE III.—AGED TWELVE YEARS: WEIGHT 71 POUNDS.

Date.	Urine sugar, gm.	Urine, diacetic acid.	Blood sugar, per cent.	Insulin, units.			Diet.			
				B.	D.	S.	C.	P.	F.	Cals.
April 28:										
6 P.M.	40.0	++++	0.312	9 P.M.—10			32	70	86	1180
10 P.M.	25.0	++++								
April 29:										
7 A.M.	30.0	++++	..	6						
10 A.M.	10						
1 P.M.	10						
4 P.M.	1.2	++++	..	10						
7 P.M.	10						
April 30	0	tr.	6	6				
May 1	0	○	0.150	6	6	6				
2	0	○	..	6	6	6	55	84	90	1366
5	0.4	○	0.115	6	6	6	100	103	141	2072
6	0	○	..	6	6	6				
9	0	○	..	6	6	6				
10	0	○	0.091							
11	Left sanitarium.									

. CASE IV.—K. B., male, aged four years, came to our institution with a history of having sugar found in the urine a week before. He had had the symptoms, weakness, thirst, polyuria, pains in abdomen, and headache for about a month, during and following an attack of influenza. Except for this attack of influenza, and colds, he had been a very healthy child all his life. When first seen he was listless and drowsy, but about average size for his age, not showing much effect of the disease in loss of weight. Physical examination was practically negative as to abnormal findings. The urine contained 1.5 per cent sugar. The blood sugar was 0.145 per cent. Diet regulation was tried, with little effect on the urine or blood sugar. Then he was given 5 units of insulin once a day, still with little effect on the condition. The dose was increased to 8 units once a day, given before dinner, the largest meal of the day. As the dosage was increased, more carbohydrate was given as cereal,

bread and potato. At once the diacetic acid of the urine disappeared, and in four days the sugar of the urine had decreased to a trace only. On the eighth day from the beginning of the 8-unit dosage, the second day of sugar-free urine, he had a hypoglycemic reaction, with great weakness, restlessness, hunger and sweating, which was almost immediately dispelled by two teaspoonfuls of Karo corn syrup in a little water. The insulin dose was decreased to 5 units once a day, and this dosage maintained for sixteen days. The urine remained sugar-free and the blood sugar ranged from 0.06 per cent to 0.085 per cent. On the sixteenth day after the first reaction, he had another similar spell of weakness, hunger and sweating, and was similarly restored by two teaspoonfuls of corn syrup in water. The insulin was then decreased to 3 units once a day, which was sufficient to maintain perfect control of the diabetes, and this was even further decreased six days later to 2 units once a day. The diet was increased as shown on the chart.

CASE IV.—AGED FOUR YEARS: WEIGHT $37\frac{1}{2}$ POUNDS.

Date.	Urine sugar, gm.	Urine, diabetic acid.	Blood sugar, per cent.	Insulin, units.			Diet.			
				B.	D.	S.	C.	P.	F.	Cals.
Jan. 31	9.0	+++	0.146	10	20	36	440
Feb. 1	4.0	+++								
2	9.0	+++								
3	12.4	+++								
4	5.0	○								
5	5.0	○								
6	4.0	++++	0.148							
7	11.0	++++	6	13	39	425
8	3.5	+++								
9	8.0	+++								
10	7.0	++++								
11	21.5	++++	15	12	24	300
12	8.0	++++	0.148							
13	11.0	++								
14	14.0	++++								
15	4.0	○	5	..	18	20	44	550
16	5.0	++++	5	..				
17	3.0	○	0.155	..	8	..	14	20	44	525
18	11.0	○	8	..				
19	10.0	○	8	..				
20	4.0	○	8	..				
21	8.0	○	8	..				
22	1.5	○	0.155	..	8	..	42	39	62	880
23	0	○	8	..				
24	0	○	8	..				
25	0	Weakness, sweating, etc...		8	Karo syrup, 5ij.			
26	0	○	5	..				
27	0	○	0.133	..	5	..				
28	0	○								
Continued same. Changes on dates noted. Insulin dosage daily.										
Mar. 5	0.060	..	5	..				
10	0.085	..	5	..	49	45	119	1450
13	..	Weakness, sweating, etc...	..	5	Karo syrup, 5ij.			
14	3	..				
15	0.098	..	3	..				
18	3	..	49	45	94	1220
20	0	0	0.076	..	3	..	49	45	94	1220
20	Left sanitarium.									

This improvement under insulin, permitting decreasing dosage of insulin, shows how the sugar burning mechanism of the body may recuperate its powers when part of the load on the pancreatic function is taken by insulin. It even justifies the use of insulin in early cases of rather acute onset, to spare pancreatic function during the acute stage of the disease, although later insulin may be discontinued and diet alone be used in treatment.

The parents of this child were very intelligent and coöperated with us in every respect. The boy did not like vegetables, and they did much coaxing to make him eat any. (We insist on the use of vegetables, because we long ago found that the green leaf vegetables have some specific properties which are good for the diabetic apart from the food value.) The boy was allowed to go home, taking 2 units of insulin once a day. After a month of perfect control of the diabetes at home, we tried having him take 2 units every other day, with some success for a while, but unfortunately a cold upset his tolerance a little and it was necessary after several trials at every other day, to go back to the daily dosage of 2 units. This dosage has been kept up generally, until the excitement and pain of having the blood taken for analysis, seemed to upset tolerance further, and it was necessary to increase the dose of insulin to 6 or 8 units when sugar showed in the urine. Once there was a hypoglycemic reaction and the next dose was omitted. He was recently brought back to the sanitarium for observation for a few days. He has gained a little in weight, much in strength, plays as any normal boy his age, and looks indeed the picture of health. It is necessary, however, to give 5 units once a day to control the diabetes at present. Perhaps this can again be decreased to the lower dosage. It is now more than nine months since the onset of the disease.

CASE V.—H. W. B., male, aged twenty-four years, has been employed as a clerk in the office of the sanitarium, where he has been kept under constant observation for eight years. During most of this time he has kept the disease under control, though at times his blood sugar has ranged high when suffering from colds, boils, etc. He was getting along well until early in February, 1923, when he began to have small boils and pimples. Blood sugar at that time was 0.18 per cent. His diet was changed in the attempt to reduce the blood sugar somewhat and the boils were carefully treated. One crop had appeared and healed, when a boil appeared on the back of the neck, about $1\frac{1}{2}$ inches below the external occipital protuberance. He attempted to pick it open himself. It failed to subside, and he reported for treatment. The boil then was in the center of an indurated, inflamed area about 4 inches in diameter. The posterior cervical glands were swollen and tender. The boil was opened widely under apothecin anesthesia, and some thick white pus was evacuated. The next two days it seemed to do better, then took

a turn for the worse. The patient was then beginning to feel some effects of the infection, being feverish, chilly, losing some weight, feeling weak, and showing much sugar in the urine. There was a profuse discharge of pus, so that bandages were soaked in a few hours. At this time insulin was begun, one day 10 units were given, the next three days two 10-unit doses daily, and finally 10 units three times a day. The blood sugar was 0.214 per cent after the first dose of insulin. Three days after the beginning of the 30-unit daily dosage, the urine became free from sugar. The blood sugar declined very slowly. At four day intervals it was successively, 0.204 per cent, 0.194 per cent, 0.177 per cent, 0.167 per cent and 0.131 per cent. It reached normal by the twentieth day. The diet was started at 22 gm. carbohydrate, 63 gm. protein, 66 gm. fat, 938 calories, and gradually increased to 44 gm. carbohydrate, 90 gm. protein, 90 gm. fat, 1450 calories, this latter diet by the time the blood sugar reached the normal mark. Within about four days from the beginning of improvement under insulin, the pus discharge began to lessen. The abscess cavity was thoroughly cleaned twice daily of all the dead tissue it was possible to reach, irrigated with 1:3 hychlorite-glycerin, and filled with the same solution. Care was taken to avoid any pressure on the inflamed area. At the end of one month from the very beginning of the boil, the pocket was pus-free, and only a clear yellow serum exuded. In five weeks it was healed. From the time the blood sugar first reached normal, the patient has remained free from sugar in the urine, has kept the blood sugar near the normal level, except in very few instances. There have been no more boils. He has gained about 20 pounds in weight. He has been able to work, and now is feeling as well as ever. The diet was finally increased to 78 gm. carbohydrate, 98 gm. protein, 145 gm. fat, about 2000 calories. His present dosage of insulin is 42 units daily.

This case illustrates the favorable effect insulin has in controlling diabetes rapidly, and raising tissue resistance in local infections. Thorough control of the disease in preinsulin days was almost equally successful, but control by diet alone under conditions of infections was much more difficult, and at times seemed impossible. Where infection has become generalized, insulin has had little effect in improving tissue resistance. Its use is recommended in cases of severe boils, carbuncles, gangrene, and in preparation for surgical operations. If acidosis is eliminated, the urine kept free from sugar, and the blood sugar nearly normal, surgery becomes far less of a peril to the diabetic than ever in the history of the disease.

In this case it has been necessary to increase the insulin daily dosage from 30 to 42 units, without much change in diet. He has gained 20 pounds of weight. It is possible that the increased body-weight constitutes that much of an overload on the sugar-burning mechanism. This would suggest care in avoiding very large gains

in weight. Our opinion is that diabetics are better slightly under the average weight for size and age, rather than fully up to the average or at all overweight. Gain in strength is to be desired, and is usually forthcoming coincident with thorough control of the disease. We do not believe that insulin should ever be given to patients who are able to eat a full maintenance diet without it, purely as a license to eat more, and take on more weight, or satisfy an abnormal appetite.

CASE VI.—J. M. S., male, aged forty-nine years, by occupation a banker, was generally healthy during childhood and early adult life. Diabetes was diagnosed in 1911, after some of the symptoms had been present as long as two years. He had had treatment under various physicians and at several sanitariums, and for the most part of the time had gotten along fairly well.

Present Illness. In the fall of 1922, he began to complain of tiring very easily. When examined a few weeks later by his physician at home, he was found to have a general anasarca, with edema up to the level of the ribs, and possibly 1.5 gallons of fluid in the abdomen. He was given a diuretic. The anasarca subsided. He went back to work. In January, 1923, he fell sick with influenza. After two weeks he had a vomiting spell lasting one and a half days. After an interval of two or three days, there was another vomiting spell. These came more often. With careful feeding, after a preliminary fast to rest the stomach, this vomiting was checked. During the time he was given strychnin and digitaline for stimulation, and codein for sleep.

He entered our institution the last day of February.

Physical Examination. The general appearance, was that of a thin, wasted, pale, weak, restless individual, without appetite, depressed and discouraged. The heart muscle tone was fair only. A late systolic murmur was heard, best at the apex, very faintly elsewhere. The blood-pressure was 124/90.

The lungs showed harsh breathing and whistling over primary bronchi, but otherwise were negative. On the abdomen, a burn from a hot-water bottle had left a superficial abscess in the wall of the epigastrium, still draining somewhat. The skin was dry and scaly with a few papules and small vesicles on legs. There were no other abnormal findings on physical examination.

Laboratory Examination. Urine: Albumin, 0.23 per cent; sugar, 1.4 per cent; diacetic acid, none; hyaline and granular casts, abundant. Blood: Sugar, 0.262 per cent; urea, 52 mg., creatinine, 2.6 mg., plasma chlorides, 525 mg. per 100 cc of blood. Kidney Function: Phthalein, 0 in two hours, only a faint tinge of color.

Daily excretion of sugar was 4 to 6 grams.

Course. Insulin was begun, 8 units three times a day. He was given about 25 gm. of carbohydrate in the diet. Within forty-eight

hours after insulin was begun, he had a severe reaction. The urine had been showing sugar present continuously. He felt a little weak after the breakfast and dinner doses of insulin, but aside from weakness, showed no other unusual signs, except a sharp fall in blood-pressure to 90/72 after breakfast. He was stimulated somewhat with aromatic spirits of ammonia, as we did not recognize the fall of blood-pressure as any indication of an insulin reaction about to occur. About two hours after the evening meal, which contained well cooked oatmeal, cream, and vegetables, and two and a quarter hours after the insulin injection, he suddenly became very restless, complained of pain in the epigastrium, began to sweat profusely and also complained of feeling very faint and weak. An ounce or two of Karo syrup in water was given by mouth, almost forced, as he was barely able to swallow. He rallied somewhat, then relapsed a little. More syrup was given, and repeated several times before he recovered. In all about 5 ounces of syrup were given. On account of the urgency of the case, no blood sugar was taken during the reaction.

The next morning, the blood sugar was 0.27 per cent. No insulin was given the next two days. The blood-pressure rose to 124/86 by the second day. Then insulin was again started, this time only 3 units once a day, increased after two days to 3 units three times a day. This dosage was sufficient to clear the urine of sugar, reduce the blood sugar to normal and keep it so, even with increase of diet, during the entire next month. The urea declined to 18 mg., the creatinine to 1.8 mg. The amount of albumin in the urine decreased slightly. He gained some in strength and his appetite improved. The sinus in the abdominal wall in the epigastrium healed. Shortly afterward, however, there appeared on the back and in the groins, vesicles and pustules, some quite deep. Under treatment, these dried up under hard scabs which persisted. About four weeks later induration and abscess formation appeared at the top of the anal crease. This was opened, with discharge of pus, and was cleaned out. Soon afterward, he began to weaken, lose appetite again, and there was a flare-up of the kidney condition, as evidenced by increase of albumin in the urine, increase of the nitrogenous elements in the blood, and the appearance of red blood cells and pus in the urine. The heart was supported with digitalis, and stimulated with aromatic spirits of ammonia as needed. Further evidence of a general infection was shown a few days later in the swelling of the left parotid gland. After two days this subsided, though there was no sign of any discharge into mouth or throat. The patient continued to weaken. A day later he died. Sugar showed in the urine only once above a trace, that in the last week of life.

Insulin was used in this case, largely in order to be able to use a diet with minimum protein and fairly large carbohydrate content on account of the nephritis. The experience with the hypoglycemic

reaction so soon after the beginning of insulin, even starting with a blood sugar of 0.262 per cent, is interesting in the light of some of the recent research on insulin. It has been shown that insulin is excreted in the urine. Cases with deficient kidney function would accordingly be expected to have a delayed or diminished excretion of insulin in the urine, and consequently more of a cumulative action. Such may be the explanation of the powerful action of insulin here shown, rather more than might have been expected from the severity of the disease. The hypoglycemia in spite of a fair intake of carbohydrate food, may have been due to slow digestion and poor absorption incident to a much weakened and run-down condition. The delayed effect of the syrup in restoring the patient from the insulin shock may also be explained as due to slow absorption of the sugar from the stomach and intestine. In such cases it is best to give glucose intravenously. In similar cases, it is also advisable to begin insulin with very small doses, even 1 or 2 units a day, and increase as needed for effect.

CASE VI.

[illegible]

Summary. We draw our conclusions not only from these cases here reported, but also summarize our experience with about 90 cases treated with insulin.

1. **AIMS IN TREATMENT.** The aim in treatment is to keep the patient with urine free from sugar, with blood sugar normal or very close thereto, and with a diet sufficient to maintain him without undernutrition, and allow him to do light work at least. If we can accomplish this without insulin, by diet regulation alone, we do not use insulin. If it is required, we give insulin in sufficient dosage to accomplish these purposes. We seek to give every patient, by oral and practical instruction, all the knowledge of the nature and administration of insulin necessary to allow him to use it intelligently. Diet regulation is fully explained, demonstrated, and thoroughly rehearsed, so that every patient should be able to keep himself in good condition.

2. **ADMINISTRATION OF INSULIN.** The insulin used has always been the product made by the Eli Lilly Co., called *iletin*.* Insulin has been generally given by the subcutaneous route. In one case of coma, it was given also intravenously. We have noticed practically no local reactions, except in a very few cases where the patient scratched the arm at the site of injection. This was apparently due to the irritation of the scratching rather than any reaction of the insulin itself. The injection of insulin has been given with $\frac{3}{4}$ -inch needles, and made thoroughly under the skin, and in no case, as far as possible, in the layers of the skin. The needles used have been 25- or 26-gauge. Alcohol has been used as the cleansing agent for the site of the injection. As to the frequency of injection, we have judged that by the individual case. Some have seemed to do better with two or three smaller doses a day, rather than one large dose. In general, however, where only 5 or less units a day have been given, it has been at a single dose before dinner or supper. We try to keep the number of injections per day as small as possible, trying the effect of two moderate doses a day rather than three small ones, being guided by the patient's response to the insulin treatment nevertheless. Where doses over 20 units per day have been given, it has been in divided doses, one-third of the daily dose before each meal. The total daily dose has varied from 2 to 88 units. We give insulin generally within twenty minutes before the meal. We have given it between meals to patients with high blood sugars at the beginning of treatment, controlling its use by analysis of the urine, and stopping its use between meals when sugar disappeared from the urine. Each patient is taught to inject the insulin into himself, except in the case of young children. Any skin area accessible is used, provided the skin is loose, but preferably the arms, forearms, thighs and legs. The dose is always taught in

* This paper was accepted in 1923, when the H-iletin, was still in use.

units, not in cubic centimeters. No practical rule has been found for determining dosage according to total glucose intake in the diet. In general we have started with small doses, 5 units once or twice a day, with diet about 1200 calories, then under guidance of urine and blood tests, increased or decreased as needed. Each patient must demonstrate his proficiency in self-administration of insulin before being allowed to go home and use it without supervision. He is expected to report in writing at weekly or bi-weekly intervals. He is expected to test the urine daily, and to keep sugar-free.

3. REACTIONS OF HYPOGLYCEMIA. We have had few reactions of hypoglycemia. We have tried to avoid such as far as possible, partly to avoid any chance of harm to the patient and partly because such happenings undermine the patient's confidence in the insulin treatment and sometimes militate against full coöperation of patient and physician. We have tested the urine hourly, or at each voiding, when using large doses of insulin, or when giving it at less than five hour intervals, or between meals, or in cases of precoma. As long as the urine has contained sugar, we have felt justified in continuing the dosage of insulin, but have diminished the dose when the urine was free from sugar, either by diminishing each dose or by discontinuing the doses between meals. Of course, the blood sugar was taken at the beginning of every treatment, to determine whether the sugar in the urine were associated with hyperglycemia or not, in order to check on the use of urine analysis as a guide in treatment. The blood sugar has been taken usually every three to five days, though in severe cases with large dose of insulin, even every three hours. The symptoms noted in hypoglycemic reactions have been similar to those reported by other observers, that is, weakness, extreme hunger, trembling, sweating, collapse. While we have not verified our observation in the case reported here, it was noticed that an abrupt fall of blood-pressure preceded other symptoms by nearly twelve hours. If such is found to be constant in rapid reduction of blood sugar, it may become a valuable early sign of over dosage of insulin. We have noticed slight fall of blood-pressure in other cases in beginning insulin administration, though never a very large or abrupt fall as long as there was no reaction. We have used corn syrup or glucose solutions to combat hypoglycemia, or allowed patients to carry or keep near at hand an orange or piece of candy.

As to possible bad effects of hypoglycemia, we may mention one case under observation at present. This patient had taken insulin at home, administered by his family physician, and had had several attacks of "shakes," or hypoglycemic reactions. He developed a rather acute heart weakness, with signs of beginning pulmonary congestion, tachycardia and complete prostration. It is quite possible that overutilization of glucose in the body may have depleted the heart reserve of glycogen or even interfered with the heart's utilization of glucose, and the myocardial weakness followed

as result of undernutrition of the heart muscle. He is beginning recovery with prolonged and complete rest, good feeding, including the use of orange juice, with just enough insulin to control the diabetes, and the use of a small dose of digitalis. Another case showed auricular fibrillation and acute heart weakness with large dose of insulin, which was completely restored by the use of orange juice twice a day together with some insulin, in decreased dose, in addition to a moderate diabetic diet, plus moderate amount of digitalis. We have not observed a sufficient number of such cases to draw any conclusions, but suggest this as a point to be watched and studied in detail. We shall proceed cautiously in cases giving history of any heart disease, when it becomes necessary to give such patients insulin.

4. COMA. We have had one case of deep coma, which was fatal in spite of insulin. This patient had 150 units of insulin within seven hours, together with glucose and digitalis intravenously, and abundance of fluid by mouth. He had an acute onset of pains deep in the epigastrium, without rigidity, and went into coma rapidly. He had had diabetes about one year. At one time after lapsing into coma he was brought back to dim consciousness, but in spite of redoubled efforts, relapsed soon into further coma. No post-mortem examination was possible, but it would have been of interest to know what pathology was present in the abdomen, possibly some acute disturbance of the pancreas (?). Other cases of beginning coma, have been restored by large doses of insulin, 10 units every three hours or oftener, with some carbohydrate being given by mouth usually, though a few of these were given insulin with a very small intake of food of any kind.

5. TOTAL DIET ALLOWED. We have not attempted to feed patients diets larger than 2400 calories daily as maximum. It has not been deemed wise to encourage the use of diets large enough to produce marked and rapid gain in weight, so long as the diets were complete in quality and quantity of the nutrients, including salts and vitamins. The diabetic cannot always be trusted with his appetite without limit, and the overfeeding which first broke down carbohydrate metabolism, if indulged in again, may well break down some other body mechanism for which we have no such convenient prop as insulin. We have kept the protein intake relatively low, ranging from $\frac{2}{3}$ to 1 gm. per kilo of body-weight, exceeding this only in growing children, to whom we have given as high as 2 gm. per kilo. As to fat we have not used the extreme high-fat diets proposed by some authorities. Very large amounts of fat are objectionable as unpalatable and therefore distasteful to most patients. We have kept the fats in the diets more nearly in the Woodyatt ratio of fatty acid to glucose of 1.5. We have fed as much carbohydrate as possible in the form of vegetables, especially the green leaf vegetables. We have found that diabetics do better when a

generous amount of the raw leaf greens, together with cooked vegetables of both leaf and root variety, is included in the diet. We are preparing considerable evidence, both clinical and laboratory, for publication, that green leaf vegetables have a specific antidiabetic effect. We use vegetables as a source of starch up to 48 gm. of carbohydrate per day, then add fruits up to 80 gm. of carbohydrate daily, then the starches of cereal or bread or potato.

6. THE QUESTION OF KEEPING THE URINE SUGAR-FREE. We have endeavored to keep the urine sugar-free and the blood sugar as near normal as possible, with insulin cases as well as with purely dietetic cases. By not using extreme doses of insulin, by dividing the daily dose into two or three parts, by using more carbohydrate in the diet rather than large amounts of fat, we have had no trouble with hypoglycemic reactions even when patients administer insulin to themselves at home. Where sugar appeared in the urine of patients taking insulin at home, some slight decreases in diet have worked as well as increases in insulin in controlling urine and blood sugar.

7. INDIVIDUALITY OF PATIENTS. There is as much necessity of individualization of treatment with insulin as it has been with diet alone. Patients differ widely in their response to insulin. While one patient will keep stationary as to progress of the disease, and keep the blood normal for months with constant dosage of insulin, others will admit of decrease in quantity of insulin, while still others will require increase of dosage to marked degree in order to keep the blood sugar down, the diet remaining the same. With the same patient at different times, he may at one time have hypoglycemic reactions with doses which will scarcely be sufficient to control the disease at other times, the diet also remaining unchanged. So, with insulin, even more than with diet alone, accurate control and careful observation are requisites of success.

8. MORTALITY RECORD OF CASES TREATED WITH INSULIN.

Total number of cases treated with insulin	92
Improved, disease controlled	85
Deaths, total	7
Diabetes: primary cause of death	2
Complications: primary cause of death, diabetes	
secondary	5
	<hr/> 7

Of the two cases with diabetes as primary cause of death, one was Case III here reported. His disease was perfectly controlled, after recovery from the verge of coma, while in sanitarium under treatment. His mother had had a brother die from diabetes, felt that the case of her boy was hopeless eventually, in spite of his favorable progress, and discontinued not only insulin but diet treatment after a week or so at home. The other case was the one mentioned as

being in deep coma. He had been under treatment only forty-eight hours when he was seized with epigastric pain and went suddenly into coma.

Of the cases with complications, one was Case VI here reported, with chronic nephritis and pyogenic infection as causes of death, the diabetes being under control at the time. Complications in the other cases which were primary causes of death were heart and gall-bladder disease, cystitis with terminal bronchopneumonia (patient aged seventy), pyemia with multiple abscesses. One of these patients had discontinued insulin more than a week before death.

AN OUTLINE OF A ROUTINE FOR INSULIN THERAPY.

BY LEON JONAS, M.D.,

AND

JOHN H. MUSSER, JR., M.D.,

PHILADELPHIA.

(From the Medical Division of the Hospital of the University of Pennsylvania.)

THE following outline of a routine for therapy in diabetes mellitus has been used by us in our clinical instruction of physicians in the use of insulin. The outline does not in any way pretend to be original, but is a compilation of the original work of many investigators and of our own studies which in our experience have given us the most satisfactory results; nor does the outline lay claim to being the only successful method of handling the diabetic patient who requires insulin. We appreciate that there are many satisfactory methods of treating these individuals and we fully comprehend that such a plan of treatment can only be tentative and subject to change as further knowledge accrues with increasing experience with insulin.

The statements we make are dogmatic. We do not feel that there is place for controversial matter in such a set of notes as we have prepared for the use of the physician who has opportunity to see only an occasional diabetic. We do feel that any physician who employs this scheme of treatment should familiarize himself with the writing of men such as Banting,¹ to whom all honor is due as the discoverer of insulin, together with his co-workers in the Toronto School. He should acquaint himself with the work of Woodyatt³ and Shaffer² on the physiological chemistry of diabetes and with the splendid text-book of the clinician, Joslin.⁴ To these men we are indebted for much of the material in this brief outline as well as to the tables of food values of Atwater and Bryant and of the Connecticut Agricultural Experiment Station.

CLASSIFICATION
 RULES FOR TREATMENT
 INSULIN TREATMENT
 KETOGENIC-ANTI-KETOGENIC
 BALANCE

DIETS
 FOOD VALUES
 HEIGHT, WEIGHT TABLES
 NORMAL CALORIC REQUIRE-
 MENTS

Classification. Unless there is clearly an only temporary glycosuria the presence of sugar in the urine should, for practical purposes, be considered as establishing a diagnosis of diabetes mellitus. In the handling of patients outside the hospital reliance must be placed upon those tests which may be readily carried out in the patient's home or physician's office. For that reason the following suggestions are adapted to conclusions which can be drawn from the clinical condition of the patient supplemented by qualitative examinations of the urine for sugar and diacetic acid. In some instances blood-sugar determinations are also used in determining the treatment.

On the basis of these examinations two classes of diabetics not under satisfactory therapeutic control can be recognized.

A. Cases with no diacetic acid in the urine or only traces, but with sugar in the urine, or with a fasting blood sugar above 0.15 per cent.

B. Cases with marked diacetic acid in the urine as well as with sugar in the urine.

Rules for Treatment. A. CASES WITH NO DIACETIC ACID OR WITH ONLY TRACES IN THE URINE, BUT WITH SUGAR IN THE URINE OR WITH FASTING BLOOD SUGAR ABOVE 0.15 PER CENT. 1. Determine normal weight for age, sex and height (see tables, page 598).

2. Place the patient on a diet of Type No. 1. The diets in the tables are prepared for patients of 100 pounds normal weight. A diet of Type No. 1 furnishes 0.5 gm. of protein and 8 calories per 1 pound. On this diet, if the diabetes is not too severe, the patient should in a few days become sugar-free.

3. If not sugar-free in three days on diet of Type No. 1 resort to insulin (see paragraph 5, page 588).

4. If the patient becomes sugar-free without insulin:

(a) If normal in weight increase diet gradually to diet of Type No. 2, 3 or finally 4, until the caloric requirement for the patient's activity and normal weight is being furnished or until sugar appears in the urine. Each of these diets when proportioned for the patient's normal weight furnishes 0.5 gm. protein per 1 pound, but increasing calories in form of fat and carbohydrate. Whatever the degree of activity of the caloric requirement of the body is being furnished the protein requirement is the same. It is higher (about 1 gm. per 1 pound), however, in children. If possible, even if there be no sugar in the urine, a fasting blood-sugar determination should be made once a week and should not exceed 0.15 per cent. When carbohydrate tolerance is reached before the desired caloric requirement is furnished fat may be increased in the diet to the maximal limit, as indicated by the following equation:

$$F = 2C + 0.5P$$

(F, C and P = gm. of fat, carbohydrate and protein respectively.)

Appearance of diacetic acid in the urine in more than occasional traces demands a diminution of the fat in the diet. If the caloric requirement is still not reached and if the patient is losing weight when the fat has been increased to the maximal limit for the protein and carbohydrate of the diet, resort to insulin treatment (see paragraph 5, page 588).

(b) If the patient is over the normal weight for age, sex and height do not exceed a diet of more than 10 calories per 1 pound (Type No. 1 with the maximal fat or Type No. 2) until normal weight is reached. Then proceed as in (a). An exception is to be made when overweight is the result of edema; edema may be due to undernutrition.

(c) If the patient is greatly under weight, and the carbohydrate tolerance permits, the diet may be in excess of the caloric requirement to encourage return to normal weight.

5. *Use of Insulin in Cases of Class A.* Insulin is indicated in all cases where the carbohydrate tolerance is not sufficient to permit a calorically adequate diet. Insulin is destroyed when introduced into the digestive tract and cannot be effectively given by mouth. It should be given hypodermically.

The dose of insulin is that required to enable the patient to utilize the carbohydrate necessary for a calorically adequate diet and remain free from glycosuria and diacetic acid in the urine and retain a fasting blood sugar below 0.15 per cent. This requires insulin sufficient to care for all of the carbohydrate required in excess of the carbohydrate tolerance of the patient. It is approximately true that 1 unit of insulin will care for 2 gm. of carbohydrate in excess of the patient's own carbohydrate tolerance. The insulin should be given twenty minutes before the carbohydrate which it is to balance. No absolute rule as to the timing of insulin dosage can be laid down at present. In patients who are up and around distribute the dosage of insulin as follows: If not more than 15 units are necessary to keep the patient sugar-free give the dosage before breakfast. If larger doses are necessary give the doses morning and night up to 30 units at each injection and give the bulk of the COH with these two meals. If doses of more than 60 units a day are given it is usually necessary to give insulin before each meal. It will not be found necessary to give insulin before the midday meal, unless large daily doses are required, because the curve of blood sugar reaches its lowest level at midday if the major part of the insulin is given in the morning before breakfast.

The determination of the proper dose of insulin may be carried out as follows: Having increased the diet as described above to the highest fat-carbohydrate content possible without glycosuria, begin with a small dose of insulin, 5 units before breakfast. Increase the fat and carbohydrate by 20 gm. of fat and 10 gm. of carbohydrate per day until sugar appears in the urine. Examine urine passed between each meal and attempt to eliminate glycosuria by redistribution of the carbohydrate with relation to the insulin dosage. Next increase the dose of insulin by 5 or 10 units. When sugar disappears from the urine make further increase in fat and carbohydrate of diet. Continue alternating the increases of insulin and the increases of diet until the required caloric intake is reached.

If for any reason the insulin is to be discontinued it is imperative to discontinue the high-caloric diet and return to a low-caloric diet within the patient's own tolerance and reducing the fat as well as the carbohydrate. At the same time all physical activities must be curtailed.

6. *Insulin Shock.* If too much insulin is given for the amount of available carbohydrate, hypoglycemia occurs. Every individual reacts differently to insulin. The more rapidly the blood-sugar concentration is reduced, the greater the possibility of insulin shock.

The symptoms of insulin shock in their order of development are: Sweating, increased pulse-rate, weakness, tremulousness and nervousness, apprehensiveness, delirium, convulsions, stupor. The symptoms may appear at a blood-sugar concentration of 0.11 per cent, but usually appear at about 0.08 per cent, and become very severe when a concentration of 0.04 per cent is reached.

7. *Treatment of Insulin Shock.* If the patient can swallow give 1 or 2 teaspoonfuls of cane sugar or glucose. When in convulsions or stupor give 15 minims of epinephrin hypodermically. If the epinephrin is not effectual give 200 to 300 cc of a 5 or 10 per cent solution of glucose intravenously. The patient will recover consciousness in a few minutes. When conscious give 1 or 2 teaspoonfuls of glucose or cane sugar by mouth.

B. CASES WITH MARKED DIACETIC ACID REACTION AND SUGAR IN THE URINE. These patients are suffering from more or less disturbance of fat metabolism, with consequent acidosis and danger of coma. Such patients should be put to bed with the same precautions as to warmth and free administration of fluid as for coma cases (see below). They must be closely watched until under therapeutic control, either by a competent nurse or by several visits daily from the physician.

1. Give diet of Type No. 5 or 6, adjusted to the normal weight of the patient, and give insulin. The dosage of insulin in less serious cases may be commenced as in the cases of Class A, but usually larger doses are necessary, 10 to 20 units before each meal or even every four to six hours. If there be symptoms of impending coma treat as described in paragraph 3.

2. As soon as the urine becomes free of diacetic acid reduce the carbohydrate to that amount which is necessary to allow of sufficient calories of protein, fat and carbohydrate for maintenance. At the same time that the carbohydrate is decreased increase the fat 10 to 20 gm. a day until a ketogenic-antiketogenic ration of 1.5 or slightly less is reached. As the carbohydrate is decreased, reduce the amount of insulin to that quantity which will keep the urine sugar-free and the patient suffer no symptoms of insulin hypoglycemia.

3. *Treatment of Threatening or Developed Coma.* Provide a special nurse or attendant both day and night, preferably one trained in diabetic work.

Bed. Keep the patient in bed and warm. Avoid loss of calories through exertion or exposure; if restless protect from becoming chilled by flannel nightclothes. Every effort should be made to allay nervousness and discomfort.

Bowels. Move the bowels by one or more enemata. Cathartics should usually be avoided for fear of causing diarrhea.

Stomach. This should be free from indigestible food. With adults, when in doubt, but with children in all cases, begin treatment with gastric lavage.

The Heart. Sustain the circulation with the help of digitalis. Caffein may be given subcutaneously, or as black coffee by rectum.

Administration of Liquids. Give 1000 cc of liquids within each six hours. The liquids are to be given slowly, hot, as coffee, tea, thin broths, water. Give by mouth if possible 20 gm. of glucose and simultaneously hypodermically 20 to 50 units of insulin. Continue giving glucose, 15 gm., every hour and insulin, 10 to 30 units, every third hour unless sugar disappears from the urine. When symptoms of coma and diacetic acid in urine disappear treat as described for cases of Class B, paragraph 1. If the patient is unconscious and cannot take glucose by mouth give continuous enteroclysis of 5 per cent glucose and give insulin hypodermically, as just described. Five per cent glucose containing 10 units of insulin per 1 pint may be given intravenously.

4. *Children.* In using insulin treatment in children begin with small doses and increase cautiously. Children are very easily thrown into insulin shock.

5. *Infections.* When a diabetic patient develops an intercurrent infection, such as tonsillitis, pneumonia, gangrene, carbuncle, etc., the urine must be followed daily, as in these conditions carbohydrate tolerance tends to fall off and acidosis is prone to develop.

Ketogenic-antiketogenic Balance. On the assumption that there is a definite quantitative relation between the total glucose burned and the amount of fat that can be completely burned at the same time, various formulas have been devised to so construct a diet that the ketogenic element is not too great, and that acidosis may consequently be avoided.

Ketogenic fraction is formed by:

90 per cent of fat.

46 per cent of protein (probably less).

Antiketogenic fraction (total glucose) is formed by:

10 per cent of fat (glycerol fraction).

58 per cent of protein (utilized as glucose).

100 per cent of carbohydrate.

Hence, the ketogenic-antiketogenic ratio is:

$$\frac{K}{A} = \frac{0.46 P + 0.9 F}{0.58 P + 0.1 F + C}$$

When $\frac{K}{A}$ equals or is less than 1.5 the ketogenic substances can be completely burned and no diacetic acid will appear in the urine. When $\frac{K}{A}$ exceeds 1.5 there is a tendency to ketonemia, ketonuria, acidosis and coma.

A convenient form of the above given ratio when the maximal fat is being given, and the ratio is equal to 1.5, is the following:

$$F = 2 C + 0.5 P$$

DIACETIC ACID TEST. The simplest method for the detection of acidosis by urinary examination is Gerhardt's ferric chloride reaction for diacetic acid. The test may be performed as follows: To about 10 cc of the fresh urine carefully add a few drops of an undiluted aqueous solution of ferric chloride (Liquor Ferri Chloridi, U. S. P.). A precipitate of ferric phosphate first forms, but upon the addition of a few more drops is dissolved. The depth of the Burgundy-red color obtained is an index to the quantity of diacetic acid present. One may record the intensity of the reaction as follows: +, ++, +++ or ++++.

Confusion as to the significance of the test arises if the patient is taking sodium salicylate, aspirin or allied products. This is to a considerable extent avoided by vigorously boiling the urine after the addition of the ferric chloride, when the deep color markedly decreases or disappears if caused by diacetic acid, but remains the same if caused by the above drugs.

INDEX OF DIETS.

	Food quantities for normal weight of lb.	Protein per lb. gm.	Calories per lb. gm.	Ketogenic- antiketogenic ratio.
No. 1 as given . . .	100	0.5	7	1.2
No. 1 max. fat . . .	100	0.5	9	1.5
No. 2 as given . . .	100	0.5	14	1.3
No. 2 max. fat . . .	100	0.5	17	1.5
No. 3 as given . . .	100	0.5	19	1.3
No. 3 max. fat . . .	100	0.5	22	1.5
No. 4 as given . . .	100	0.5	25	1.3
No. 4 max. fat . . .	100	0.5	28	1.5
No. 5 as given . . .	100	0.5	11	0.2
No. 6 as given . . .	100	0.5	11	0.1

Diets. The following diets are for a person weighing 100 pounds.

Numbering is purely arbitrary and has no relation to the order in which the diets should be given. It is particularly important to note that the severe cases should be started on Diet No. 6.

Increase or decrease the meat so that the patient receives 0.5 gm. per pound of body weight. Patients admitted with a glucosuria but without diacetic acid are placed on Diet No. 1. Increase the diet as guided by urine examinations.

The quantity of vegetables in each diet is relatively low, so that 10 or 15 gm. of carbohydrate may be added to the diet as vegetables without making too great a bulk. If it is desired to add more than this amount use the next higher diet.

Fat may be increased up to maximum mentioned in each diet and still be within the safe range of ketogenic-antiketogenic ratio.

Diet No. 1.

Breakfast:		P.	F.	C.
Grapefruit	150 gm.	0.6	..	5.7
Eggs	2	13.2	12.0	
Coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		14.0	12.0	5.7
Dinner:				
Broth	150 cc	3.5		
Lean meat	100 gm.	23.0	28.6	
Vegetables, 5 per cent	100 gm.	0.5	..	4.0
Vegetables, 10 per cent	100 gm.	0.5	..	8.0
Tea or coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		27.5	28.6	12.0
Supper:				
Egg, with lettuce as salad	1	6.5	6.0	
Coffee				
Oatmeal	50 gm.	1.4	0.2	5.8
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
Total		49.0	46.0	23.0
Total calories, 700				

Maximum fat permitted when urine is sugar-free, 70 gm.

If the patient does not become sugar-free place on Diet No. 2 and use insulin. See details of insulin treatment.

Diet No. 2.

Breakfast:		P.	F.	C.
Grapefruit	150 gm.	0.6	..	5.7
Egg	1	6.5	6.0	
Oatmeal	100 gm.	2.8	..	11.5
Butter	15 gm.	..	12.7	
Cream	20 cc	0.6	5.0	1.0
Coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		10.5	23.7	18.2

Dinner:		P.	F.	C.
Broth	150 cc	3.5		
Meat	100 gm.	23.0	28.0	
Vegetables, 10 per cent	100 gm.	1.0	..	8.0
Vegetables, 15 per cent	100 gm.	1.0	..	12.0
Cream, 20 per cent	15 cc	1.6	3.0	1.2
Butter	15 gm.	..	12.7	
Tea or coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		29.1	43.7	21.2
Supper:				
Eggs	2	13.2	12.0	
Bacon	15 gm.	0.7	9.0	
Vegetables, 10 per cent	100 gm.	1.0	..	8.0
Vegetables, 5 per cent	100 gm.	1.0	..	3.0
Butter	15 gm.	..	12.7	
Cream, 20 per cent	15 cc	0.6	3.0	1.2
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		16.5	36.7	12.2
Total		56.0	104.0	52.0
Total calories, 1370.				

Maximum fat permitted 130 gm.

When higher amounts of carbohydrates are desired work up to Diet No. 3.

<i>Diet No. 3.</i>				
Breakfast:		P.	F.	C.
Grapefruit	150 gm.	0.6	..	5.7
Egg	1	6.5	6.0	
Oatmeal	150 gm.	4.7	..	16.0
Butter	30 gm.	..	25.5	
Cream, 20 per cent	40 cc	1.2	8.0	2.0
Coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		13.0	39.5	23.7
Dinner:				
Broth	150 cc	3.5		
Meat	90 gm.	20.7	25.2	
Vegetables (potato)	100 gm.	2.0	..	20.0
Vegetables, 15 per cent	100 gm.	1.0	..	12.0
Vegetables, 10 per cent	100 gm.	1.0	..	8.0
Cream, 20 per cent	40 cc	1.2	8.0	2.0
Butter	30 gm.	..	25.4	
Tea or coffee				
Non-COH biscuit	2			
		<hr/>	<hr/>	<hr/>
		29.4	58.6	42.0

		P.	F.	C.
Supper:				
Eggs	2	13.2	12.0	
Bacon	30 gm.	1.4	18.0	
Vegetables, 5 per cent	100 fm.	1.0		3.0
Butter	30 gm.		25.2	
Cream, 20 per cent	15 cc	0.6	3.0	1.2
Fruit or berries	50 gm.	8.0
Coffee				
Non-COH biscuit	2			
		16.2	58.2	12.2
Total		58.0	156.0	78.0

Total calories, 1950.

Maximum fat permitted, 184 gm.

If patients remain sugar-free on this diet insulin may not be necessary; if sugar occasionally appears or blood sugar is high small doses of insulin may be desirable.

Diet No. 4.

		P.	F.	C.
Breakfast:				
Grapefruit	150 gm.	0.6	0.1	5.7
Egg	1	6.5	6.0	
Oatmeal	150 gm.	4.7	..	16.0
Butter	30 gm.	..	25.4	
Cream, 20 per cent	60 cc	1.8	12.0	3.0
Bacon	30 gm.	1.4	18.0	
Tea or coffee				
Non-COH biscuit	2			
		15.0	61.5	24.7
Dinner:				
Meat	90 gm.	20.7	25.2	
Potatoes	75 gm.	1.5	..	15.0
Vegetables, 10 per cent	100 gm.	1.0	..	8.0
Vegetables, 15 per cent	100 gm.	1.0	..	12.0
Vegetables, 5 per cent	100 gm.	1.0	..	3.0
Cream, 20 per cent	60 cc	1.8	12.0	3.0
Butter	50 gm.	..	42.5	
Olive oil (in dressing)	20 cc	..	20.0	
Fruit or berries (up to 15 per cent group)	100 gm.	1.0	..	15.0
Tea or coffee				
Non-COH biscuit	2			
		28.0	99.7	56.0
Supper:				
Eggs	2	13.2	12.0	
Rice	75 gm.	2.1	..	18.0
Cream	60 cc	1.8	12.0	3.0
Butter	20 gm.	..	17.0	
Tea or coffee				
Non-COH biscuit	2			
		17.1	41.0	21.0
Total		60.0	202.0	102.0

Total calories, 2470.

Maximum fat permitted, 240 gm.

If sugar-free on this diet insulin is not indicated.

<i>Diet No. 5.</i>				
Breakfast:				
Grapefruit	150 gm.	P. 0.6	F. ..	C. 5.7
Oatmeal	150 gm.	4.7	..	16.0
Egg	1	6.5	6.0	
Milk	50 cc	1.5	2.0	2.5
Tea or coffee				
Non-COH biscuit	2	<hr/>	<hr/>	<hr/>
		13.3	8.0	24.2
Dinner:				
Broth	150 cc	3.5		
Meat	90 gm.	20.7	25.2	
Rice	100 gm.	2.8	..	24.0
Potatoes	100 gm.	2.0	..	20.0
Vegetables, 10 per cent .	150 gm.	1.0	..	12.0
Milk	50 cc	1.5	2.0	2.5
Tea or coffee				
Non-COH biscuit	2	<hr/>	<hr/>	<hr/>
		31.5	27.2	58.5
Supper:				
Egg	1	6.5	6.0	
Rice	150 gm.	4.2	..	36.0
Milk	50 cc	1.5	2.0	2.5
Tea or coffee				
Non-COH biscuit	2	<hr/>	<hr/>	<hr/>
		12.2	8.0	38.5
Total		57.0	43.0	121.0
Total calories, 1100.				

Cases with ketonuria and glucosuria, but with a normal or nearly normal reaction of blood, give insulin as detailed under insulin treatment.

<i>Diet No. 6.</i>					
Breakfast:			P.	F.	C.
Orange	150 gm.	10.0
Oatmeal	200 gm.	6.5	..	22.0
Milk	50 cc	1.5	2.0	2.5
Coffee			<hr/>	<hr/>	<hr/>
			8.0	2.0	34.5
10.30 A.M.:					
Oatmeal	200 gm.	6.5	..	22.0
Dinner:					
Broth	150 cc	3.5		
Potato	100 gm.	2.0	..	20.0
Rice	200 gm.	5.6	..	48.0
Milk	50 cc	1.5	2.0	2.5
Coffee			<hr/>	<hr/>	<hr/>
			12.6	2.0	70.5
3.30 P.M.:					
Oatmeal	200 gm.	6.5	..	22.0
Supper:					
Oatmeal	200 gm.	6.5	..	22.0
Milk	50 cc	1.5	2.0	2.5
Coffee			<hr/>	<hr/>	<hr/>
			8.0	2.0	24.5

10 P.M.:		P.	F.	C.
Toast	25 gm.	4.0	0.5	15.0
1 A.M.:				
Toast	25 gm.	4.0	0.5	15.0
4 A.M.:				
Toast	25 gm.	4.0	0.5	15.0
		<hr/>	<hr/>	<hr/>
		12.0	1.5	45.0
Total		54.0	8.0	218.0
Total calories, 1150.				

A severe case with marked ketonuria, glucosuria and a shifting of the reaction of the blood to the acid side. Cases rapidly approaching coma. Give insulin as detailed under insulin treatment.

FOOD VALUES.

1. *Protein Foods Free of Carbohydrate and Fat.*

	P. per cent.	F. per cent.
Gelatin	90.0	
Soups:		
Broth	2.2	
Vegetable	2.0	
Egg whites	12.0	

2. *Protein Foods Free of Carbohydrate.**Low in Fat (below 10 per cent).*

Dried beef	40.0	6.0
Beef tongue	20.0	9.0
Sweetbread	20.0	9.5
Lean veal	20.0	6.0
Chicken—broilers	22.0	3.0
Fish—various, fresh	18.0	1-2
Shad, halibut and mackerel	19.0	5-9

High in Fat (over 10 per cent).

Lean beef—cooked	25.0	12.0
Beef	24.0	25.0
Mutton	25.0	23.0
Ham, lean pork, pork chops	20.0	20.0
Bacon	10.0	60.0
Chicken	20.0	16.0
Salmon	22.0	13.0
Herring	37.0	16.0
Sardines	23.0	20.0
1 egg	6.5	6.0

3. *Fats Free of Protein and Carbohydrate.*

Butter	85.0
Olive oil	100.0

4. *Carbohydrate-containing Foods, Grouped by Percentage of Carbohydrate.*

(1) Vegetables	(3) Nuts	(5) Milk foods
(2) Fruits	(4) Miscellaneous	

5 per cent Group.

	P., per cent.	F., per cent.	C., per cent.
(1) Lettuce, cucumbers, spinach, asparagus, rhubarb, sauerkraut, beet greens, dandelion, greens, Swiss chard, celery, tomatoes, Brussels sprouts, watercress, sea kale, okra, cauliflower, egg-plant, cabbage, radishes, leeks, string bean . .	1-2	..	5.0
(2) Ripe olives	25.0	5.0
Grapefruit			
(3) Butternuts	28.0	60.0	5.0
Pignolias	34.0	50.0	5.0
(4) Pickles, unsweetened and unspiced	5.0
Clams	9.0	..	5.0
Oysters	6.0	..	5.0
Scallops	15.0	..	5.0
Liver	20.0	5.0	5.0
Shad roe	20.0	4.0	5.0
Soups—tomatoes and chicken gumbo .	2-4	..	5.0
(5) Milk	3.0	3.0	5.0
Cream, 20 per cent	3.0	20.0	3.0
Cream, 40 per cent	3.0	40.0	3.0
Buttermilk	3.0	0.5	4.8
Cheese, cottage	21.0	1.0	4.0
Cheese, American, Swiss and Cream . .	28.0	38.0	3.0

10 per cent Group.

(1) Pumpkin, turnips, kohlrabi, squash, beets, carrots, mushrooms, boiled oatmeal and onions	1-2	..	10.0
(2) Lemons, oranges, cranberries, strawberries, blackberries, gooseberries, peaches, pineapples, watermelon, green olives	25.0	10.0
(3) Brazil nuts, black walnuts, hickory nuts, pecans, filberts	10-25	50-70	10.0

15 per cent Group.

(1) Green peas	7.0	..	15.0
Artichokes	3.0	..	15.0
Parsnips	2.0	..	15.0
Canned lima beans	4.0	..	15.0
(2) Apples, pears, apricots, blueberries, cherries, currants, raspberries, huckleberries.	15.0
(3) Almonds, English walnuts, beechnuts, pistachios	20.0	55.0	15.0

20 per cent Group.

(1) Potatoes	20.0
Fresh lima beans	7.0	..	20.0
Baked beans	7.0	..	20.0
Green corn	20.0
Boiled rice	20.0
Boiled macaroni	20.0
Cooked hominy	20.0
(2) Plums, bananas, prunes	20.0
(3) Peanuts	26.0	39.0	20.0

High Carbohydrate Group.

	P. per cent.	F. per cent.	C. per cent.
White bread	10.0	..	55-60
Whole wheat bread	10.0	..	50.0
Crackers, various	10.0	..	70.0

Food Values. An estimate of the quantity or bulk of food may be of assistance or interest. There is so much variation in the size of tablespoons or what may be termed either rounding or heaping tablespoons that it must be remembered that we can only estimate.

100 gram Portions.

Asparagus, 8 or 9 stalks 4 inches long.
 Beans (string) (cut in small pieces), 3 heaping tablespoons.
 Bacon, 4 slices 6 inches long, 2 inches wide.
 Cabbage (cooked), 3 heaping tablespoons.
 Cauliflower, 3 rounding tablespoons.
 Celery, 6 pieces $4\frac{1}{2}$ inches long, medium thickness.
 Cheese, a piece 4 inches long by $1\frac{1}{2}$ inches by 1 inch.
 Cucumbers, 12 slices $\frac{1}{8}$ inch thick, $\frac{1}{2}$ inch in diameter.
 Greens (spinach, kale, etc.), 3 heaping tablespoons.
 Lettuce, 10 to 12 medium sized leaves.
 Onions, 2 onions, size of an egg.
 Olives, 25 small olives.
 Peas, 3 rounding tablespoons.
 Potatoes (baked), 1 small potato, size of an egg.
 Potatoes (mashed), 2 rounding tablespoons.
 Sardines, 28 sardines = 1 small box.
 Salmon, $\frac{1}{4}$ can (almost).
 Tomatoes, $2\frac{1}{2}$ heaping tablespoons.
 Tomatoes, fresh, one medium sized tomato, 2 inches in diameter.
 Bacon loses about half of its fat content when cooked.

Other Weights.

1 tablespoon of olive oil	= 13 gm.
1 tablespoon of mayonnaise	= 21 "
1 thin slice of bread (baker's loaf)	= 25 "
1 medium sized orange	= 150 "
1 peach	= 125 "
1 medium sized apple	= 150 "
$\frac{1}{2}$ small grapefruit	= 150 "
1 medium sized lamb chop with bone	= 100 "
1 medium sized slice cold tongue	= 100 "
1 average helping of fish	= 100 "
1 average helping of butter	= 10 "
1 average sized egg	= 50 "
1 average helping of boiled cereal	= 100 "
1 potato, size of large egg	= 100 "
1 slice tenderloin steak 1 inch thick	= 100 "

It is not true that all the vegetables weigh the same, but for the sake of simplicity in most of the diets it has been reckoned that 2 heaping tablespoons of any one of the "5 per cent" vegetables weighs 100 gm.

Bran Biscuits.

- $\frac{3}{4}$ cup of Kellogg's bran.
- $\frac{1}{2}$ glass of cold water.
- $\frac{1}{4}$ teaspoon salt.
- $2\frac{1}{2}$ teaspoons powdered agar-agar.

Tie bran in a thin cloth and wash under tap until water is clear. Put the agar-agar in the cold water and heat until it comes to the boiling-point. Remove from fire and add to it the washed bran and salt. Form into small biscuit, place on a greased pan and let stand until they have become firm and cool. Bake in moderate oven thirty to forty minutes.

Agar-agar may be purchased at a drug store.

NORMAL HEIGHT-WEIGHT TABLES (LIFE INSURANCE STATISTICS).

Normal Weight for Height in Children (without Clothes).

Height.		Weight—lbs.	
Feet.	Inches.	Boys.	Girls.
2	3	18.7	18.3
2	6	22.9	21.8
3	0	30.6	30.5
3	6	41.0	40.0
4	0	53.0	51.0
4	6	70.0	68.0
5	0	93.0	100.0

Heights and Weights of Men (Weight with Clothes; Height with Shoes). Feet and Inches.

Age.	5-0.	5-6.	6-0.	6-5.
15	107	126	152	177
20	117	136	161	186
30	126	144	172	201
40	131	149	180	212
55	135	153	184	219

Women.

Age.	4-8.	5-0.	5-6.	6-0.
15	101	107	126	152
20	106	114	132	156
30	112	120	138	161
40	119	127	146	167
55	125	133	153	177

Normal Caloric Requirements.

Adults.	Calories, per lb.
At rest	11-14
Light work	16-18
Moderate work	18-20
Hard work	20-27
Children, age.	Calories, per lb.
2	36
6	31
12	23

BIBLIOGRAPHY.

1. Banting, F. G., and others: Jour. Lab. and Clin. Med., 1922, 7, 261; Canad. Med. Assn. Jour., 1922, 12, 141; *ibid.*, 1923, 13, 565; Am. Jour. Physiol., 1922, 62, 162; *ibid.*, 1922, 62, 559; Jour. Metab. Res., 1922, 2, 547; Brit. Med. Jour., 1923, 1, 8.
2. Shaffer, P. A.: Physiol. Rev., 1923, 3, 394.
3. Woodyatt: Arch. Int. Med., 1921, 28, 125.
4. Joslin, E. P.: Treatment of Diabetes Mellitus, Lea & Febiger, Philadelphia, 1923.

REVIEWS.

A MANUAL OF HISTOLOGY. By V. H. MOTTRAM, M.A., Professor of Physiology in the University of London (King's College for Women). Pp. 294; 224 illustrations. New York: E. P. Dutton & Co., 1923.

THIS book on normal histology has been prepared with a special purpose in view. The student, having his microscope and sections of tissues before him, will find here a guide in his study, both by illustration and description. The author is careful in both of these aids, not to go too far, but leaves matters so that it is necessary for the student to follow out the details for himself under the microscope. Thus, the illustrations show the pattern of the structures, carefully outlined with the aid of the camera lucida, but the details are not filled in. In the text, too, the salient features are given in an orderly manner, but not an exhaustive description of minutiae. It must be noted, however, that the author is aided in his clear exposition, and typical views of tissues, by making free use of animal tissues, which are, of course, better preserved and less variable in appearance than material from human autopsies. The plan of the book is so well executed that the author must be regarded as having made a distinct contribution to the pedagogy of the subject.

A.

PULMONARY TUBERCULOSIS—ITS ETIOLOGY AND TREATMENT. By DAVID C. MUTHU, M.D., M.R.C.S., L.R.C.P., Associate of King's College, London. Pp. 381; 28 illustrations. New York: William Wood & Co., 1922.

THIS work is entitled "A Brief Survey of the Scientific, the Sanatorium and Social Aspect of Tuberculosis."

The author, in attempting to lay stress on the importance of environmental factors in the tuberculosis problem, finds it necessary to attempt a denial of any causal relationship of the tubercle bacillus to tuberculosis. Regarding the presence of tubercle bacilli in tuberculous lesions, he goes back a half century for an explanation which is acceptable to him and a plate illustrates this theory of the development of bacilli from the leukocyte through a process of degeneration of the cell. According to him, tubercles are a physiological

endeavor on the part of the human organism to rid itself of residual substances remaining after the destruction of red cells which have been damaged by stale air and stale food. Successive crops of tubercles result in tuberculosis and with tuberculosis the bacilli are formed.

The important questions of housing, nutrition, and the sociological features of the tuberculosis problem are discussed but the work is so biased by the constant effort to deny the infectiousness of the disease that its usefulness is questionable. In a chapter on the prevention of tuberculosis, there is no mention of sputum disposal or possible infection of others by active cases of tuberculosis. It is a novel experience to find a student of tuberculosis in the present day willing to ignore so much. The restriction placed upon his writing by his views on infection must have made the writing of this book a difficult matter. T.

OPERATIVE SURGERY. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By WARREN STONE BICKHAM, M.D., PHAR.M., former Surgeon in Charge of General Surgery, Manhattan State Hospital, New York; Former Instructor in Operative Surgery, College of Physicians and Surgeons (Columbia University), in the New York Post-graduate Medical School and Hospital, and in the New York Polyclinic Medical School and Hospital. Vol. I, pp. 850; Vol. II, pp. 877; 6378 illustrations, many in colors. Philadelphia and London: W. B. Saunders Company, 1923.

THIS monographic work has attained the dimensions of a system, appearing in five volumes, of which two have just been issued. It is encyclopedic in scope and treatment. Gynecologic, obstetric, genito-urinary, orthopedic surgery and even the more highly specialized fields of the eye, ear, nose and throat are to be included. In arrangement of the text it follows closely the author's well-known single volume in operative surgery. His task is to describe in compact form the methods and technic of accepted operations together with the essentials of the surgical anatomy of the parts and to offer comments suggested by experience. The matter is boiled down to a terse and impersonal quality of statement that makes hard reading but is nevertheless good for reference purposes. In the choice of operations to be described the author has conservatively and properly held with customary practice and weight of authority. Surgeons interested in special fields or procedures may miss items which seem of great importance but it is evident that even in a work of this size the task of deletion from the great mass of available material has not been easy and in these early volumes it may

invite suggestion but no serious criticism. Illustrations are copious and excellent. Type, paper and proofreading deserve praise. It seems certain to take its place as the leading American work on Operative Surgery.

Volume I devotes about one-third of its space to pre- and post-operative considerations, to anesthesia and the general conduct of operations. This portion of a book is usually prosy to the average surgeon but it is well done and will repay perusal. The remainder of the volume is devoted to plastic surgery, amputations, excisions and prostheses.

Volume II deals with arteries, veins, lymphatics, nerves, bones, joints (other than excision), muscles, tendons, ligaments, cartilages, bursæ and fascia. This concludes the general section and is followed by the third and final section of special or regional operations of which two fields are here given, namely, the skull and brain and the spine and cord. In a spirit of coöperation the reviewer would like to see in the next edition (for there certainly will be later editions) a mention of the usefulness of tongs extension, of Willems' method of treating suppuration of the joints and would suggest deletion of the illustrations depicting rubber tubes passing through the knee joint. Also debridement can justify its inclusion among the considerations of general surgery. We would prefer incisions for removal of the palmar fascia in Dupuytren's contracture to be transverse in the natural folds rather than straight and would recommend Smith-Petersen's incision of the hip-joint. Such omissions are inconsiderable in weighing the merits of the book. Congratulations are due Dr. Bickham for a monumental piece of work which few surgeons will feel able to do without.

P.

SELECTED ESSAYS ON ORTHOPEDIC SURGERY. From the writings of NEWTON MELMAN SHAFFER, M.D., F.A.C.S., Emeritus Professor of Orthopedic Surgery, Cornell University Medical College. Pp. 636. New York and London: G. P. Putman's Sons, The Knickerbocker Press, 1923.

THESE essays, selected from writings between the years 1877 and 1904, contain principles which have stood the test of time, and have been found practical in an enormous service.

The chapters on Pott's disease, scoliosis, claw foot and fracture of the neck of the femur are noteworthy. Conservatism is the dominating feature of the book.

Historically, it is of interest to record that as far back as 1879 Shaffer taught and practised the conservative treatment of acute abscess in Pott's disease; also the necessity of proper fixation apparatus, while in 1885 he advocated and successfully treated fracture of the neck of the femur by abduction and extension.

B.

INFLAMMATION IN BONES AND JOINTS. By LEONARD W. ELY, M.D., Associate Professor of Surgery, Stanford University. Pp. 433; 144 illustrations. Philadelphia and London: J. B. Lippincott Company, 1923.

THIS book is issued with the admirable intent of the author to set forth his conceptions of etiology, pathology and treatment in a special field which he had cultivated intensively. Not all will agree with his thesis in detail but there is food for reflection and much information. The author believes that the marrow and the synovial membranes are the only two tissues actively concerned in the origination of infections of the bones and joints. The lymphoid marrow is especially vulnerable as are lymphoid structures elsewhere. The chief difference in the course of infections of the bone from other infections arises from the fact that the process is confined in a bony box. This differs from the usually accepted explanation of Lexer that infections of bone localize near the epiphysis because of the arrangement of the circulation. He believes that acute osteomyelitis is always a marrow infection, spreading first in the central canal and then perforating to become subperiosteal. He does not mention Starr's idea that the infection of the metaphysis may extend at once outward to the periosteum and kill the shaft by burrowing beneath that membrane. Ely therefore advocates immediate and wide opening of the medullary cavity. This is the usual practice, it is true, but it would be well to grant consideration to a newer conception which has been well argued. He divides arthritis into two great types according to their pathology. The first type includes frank and presumptive infective conditions; the second is the mysterious type of more advanced years and unknown etiology he believes it is due to gastrointestinal conditions and, in some cases at least, to infection with an ameba.

Debridement is hardly considered and Willems' treatment, not at all. There is no apparent attempt to make the book complete for reference. It is worth perusal as a stimulating and in some respects, novel contribution. P.

DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., LL.D., Professor of Diseases of the Skin, University of Kansas School of Medicine; Dermatologist to the Christian Church Hospital. Fifth edition. Pp. 1213; 1069 illustrations. St. Louis: C. V. Mosby Company, 1923.

SUTTON'S book, after a period of but two years, has again been revised and is now in its fifth edition. The frequency of the revisions speak well for the excellence of the publication and the popularity of the author.

There have been numerous contributions to dermatology during the last few years and the following diseases have been added to the previous edition: *alastrim*; itchy points; *erosio interdigitalis blastomycetica*; *poikiloderma atrophicans vasculare*; *melanotic whitelow*; multiple benign tumor-like new growths of the skin; Rocky Mountain fever; the pink disease; *perifolliculitis capitis abscedens et suffodens*; *wit-kop*; *ochronosis*; carotinoid pigmentation of the skin; and *hypodermiasis*.

One hundred new illustrations have been added. Six hundred additional literary references are tabulated so that with these new additions the volume contains eighty-two more pages than the previous edition. There is no dermatological treatise which is as profusely illustrated or in which so many rare diseases are depicted.

K.

HERNIA. By LEIGH F. WATSON, M.D., Associate in Surgery, Rush Medical College. Pp. 660; 232 illustrations. St. Louis: C. V. Mosby Company, 1924.

THE work takes up in detail the important features of the anatomy, etiology, symptomatology, diagnosis and treatment of hernia, together with the best operative technic of modern surgeons.

The anatomy is taken up in an exhaustive manner in order that it may be a handy reference.

The material for the text has been gleaned from the entire literature on the subject and the bibliography has been selected carefully, the majority of the articles themselves containing an extensive bibliography.

All the operations performed for hernia are not given in detail thus those of the most common use are described thoroughly while the less frequently employed ones are described in less detail.

The book is nicely gotten up, well edited, clearly written and extensively illustrated.

E.

HUMAN PROTOZOÖLOGY. By ROBERT W. HEGNER, PH.D., Professor of Protozoölogy and WILLIAM H. TALIAFERRO, PH.D., Associate Professor of Protozoölogy in the School of Hygiene and Public Health of the Johns Hopkins University. Pp. 597; 197 illustrations. New York City: The Macmillan Company, 1924.

IN the preface the authors remark that the subject matter of the course in protozoölogy as represented in this volume has been prepared particularly for the use of students. They have exercised rigid selection in material included, due to the fact that the protozoa are such an extremely large group, representing as they do a

very large number of species and individuals. For this reason the book represents only the essentials of a study of the protozoa and the protozoal diseases. It is of a size which makes it readily accessible to the physician who is interested in this very important subject, and yet it contains enough material to be of great value to those interested in the more thorough exposition of protozoölogy, while the extended bibliography in the back of the book will give this type of individual references to which he may refer for more detailed works and studies. There is a real need for such a book as this. The classification of the protozoal diseases in various text-books devoted to medicine is most diverse and frequently incorrect. Furthermore the description of many of the organisms is inaccurate. This book details what is known about protozoa and precisely shows the relation this group bear to disease and particularly to disease that occurs in man. M.

A COMBINED TEXT-BOOK OF OBSTETRICS AND GYNECOLOGY. By J. M. MUNRO KERR, M.D., F.R.C.P. and S. (GLAS.), Professor of Obstetrics and Gynecology, Glasgow University (Muirhead Chair); JAMES HAIG FERGUSON, M.D., F.R.C.S. (EDIN.), Gynecologist, Royal Infirmary, Edinburgh; Obstetric Physician, Royal Maternity Hospital, Edinburgh; JAMES YOUNG, D.S.O., M.D., F.R.C.S. (EDIN.) Examiner for the Fellowship of the Royal College of Surgeons, Edinburgh; JAMES HENDRY, M.A., B.Sc., M.B., Senior Assistant to the Muirhead Professor, University of Edinburgh. Pp. 1006; 474 illustrations. New York: William Wood & Co.; Edinburgh: E. and S. Livingston, 1923.

THE appearance of a second notable text-book within two years by British authors combining in one volume the subjects of gynecology and obstetrics is significant of the widespreading realization that one who treats diseases of women must possess a full knowledge of the mechanism and results of the physiologic processes of the pelvic organs as well as a certain surgical dexterity in treating pelvic pathology.

The book in hand is by four members of the faculties of Glasgow and Edinburgh in which they have presented the interrelated subjects in a logical manner. The material of the text, while thorough and clear, is nevertheless concise and fundamental, without the usual haze of non-essential padding.

The views of the authors are modern, yet a conservative tendency is noted throughout; as in the treatment of eclampsia, a wise caution as to undue haste in delivery, the treatment of pelvic inflammation, medically and surgically, and the too sanguine expectation of the results to be achieved by the use of radium in malignancy.

W.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

Immunological Significance of Vitamines.—Since vitamine deficiency seems definitely to reduce the resistance of the body to infections, WERKMAN (*Jour. Infect. Dis.*, 1923, 32, 247 and 255) decided to investigate the source of this break in the body protective mechanism. He first studied the production of antibodies (agglutinins, precipitins, hemolysins and bacteriolysins) in rats, rabbits and pigeons suffering from lack of vitamine-A and vitamine-B and in normal control animals. There was found no interference with the antibody formation under these circumstances. The same kind of animals were next tested as to their resistance to infection when fed on the same deficiency diet. In every case the susceptibility to infection was markedly increased when either vitamine-A or vitamine-B was absent. This lessened resistance to disease must rest when on some other basis than an altered antibody production.

The Principles of the Arseno-bismuth Treatment of Syphilis.—To avoid the troublesome and sometimes dangerous stomatitis, which occasionally follows the use of bismuth in syphilis as introduced by Sazerac and Levaditi, it is advised by SEZARY and POMERAT (*Med. Press and Circ.*, 1923, 166, 298) that tartrobismuthate be mixed with arsenobenzol just before injection into the muscle. The stomatitis itself responds readily to the action of the arsenobenzol locally or internally. They accomplish the mixing of the two drugs in the syringe just before injecting by drawing up solutions sufficient to give 0.12 gm. of the amino-arseno-phenol and 0.1 gm. of the tartrobismuthate. The amounts of the two may be varied as desired, but the mixing should only be made just before injecting, as the resulting

compound is unstable. Not only does no stomatitis appear when this mixture is used, but the bismuth gum-line rarely is seen, even when the injections are repeated as often as three times a week. The toxicity of the bismuth seems greatly reduced by this association with arsenic, while the treponemicidal action of the mixture is higher than that of either constituent alone.

Bronchopneumonia Following Measles Cured by Artificial Pneumothorax.—BERNARD (*Bull. et mém. Soc. méd. d. hôp. de Paris*, 1923, 39, 1638) describes a most interesting instance of acute unilateral bronchopneumonia in a child, which came on following measles. The condition was so serious as to give rise to the suspicion in the mind of one of the consultants of a possible acute tuberculosis. Roentgenograms showed the left lung filled with scattered shadows of a moderate density with rather hazy borders, somewhat smaller than a ten-cent piece. The shadows at the hilus were not beyond those one ordinarily sees in healthy children. In response to the urgent request of his colleague, Bernard performed an artificial pneumothorax on the left, introducing 200 cc of nitrogen and 100 on the following day when the collapse of the lung was complete. On the day following this, the temperature fell sharply; with a slight rise two days later, followed by a third insufflation. Thereafter, the temperature remained normal, the pulmonary collapse was maintained, but two more insufflations were made on June 19 and 22. By June 25, thirteen days after the first insufflation, the child was perfectly well and the lung entirely clear. In other words, a child with a bronchopneumonia following measles, who was in an exceedingly grave condition, recovered as if by magic following an artificial pneumothorax. Bernard reports the case merely as an experience worth considering in the future.

Disappearance of Chlorosis.—An interesting discussion took place recently at a meeting of the Société médicale des hôpitaux, apropos of a communication by RIST (*Bull. et mém. Soc. méd. d. hôp. de Paris*, 1923, 39, 1563) on the disappearance of chlorosis. In addition to the speaker, Chauffard, Achard, Hallé, Fiessinger and Ramond all added their testimony to that of various observers in this country, in Scandinavia, in Switzerland, England, Germany and Austria, that chlorosis, a malady so frequent thirty years ago, has become today, at least in its outspoken forms, a relatively rare disease. No adequate explanation of this phenomenon which has been noted by all physicians of many years' experience in this country, has been offered. PINARD (*Ibid.*, 1574) raises the question as to whether its disappearance may not mean simply an increase in our diagnostic powers which lead us properly to classify conditions which previously had been roughly classified as chlorosis. This may be true for a certain number of cases. It is not impossible that many instances of secondary anemia dependent on focal infections were in older days classed as chlorosis; but it is rather hard to believe this is the only explanation.

Observations on Changes in the Size and Shape of Hearts during the Progress of Compensation.—Twenty-one cases of decompensation, due both to endocarditis and myocarditis, were observed by FRIEDMAN and STRAUSS (*Arch. Int. Med.*, 1923, 32, 601). Successive roentgeno-

grams, taken in the course of the hospital stay, were superimposed on each other, and the results compared with the figures obtained by percussion. On the whole, the two methods gave concordant figures. It was found that compensation may be regained without any change in the diameter or shape of the heart. The most frequent changes noted were at the base, involving especially the vena cava and pulmonary artery. The left cardiac border rather strikingly showed little retraction compared with the right. Cases in which several breaks in compensation were observed showed involvement of different divisions of the heart at each period, although the clinical picture was the same.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Carcinoma of Lingual Thyroid.—TYLER (*Jour. Radiol.*, 1923, 4, 381) says that lingual thyroid is a tumor in the root of the tongue, due to a failure of the thyroid to entirely migrate to its normal position during embryonic development. Histologically and clinically it has the characteristics of the thyroid. It is most frequently found in women, (forty to fifty years of age) being the proportion in reported cases. It may undergo malignant degeneration and metastasize through the blood stream. Surgical enucleation is the best treatment. Roentgen-ray and radium treatment are beneficial in cases where surgical removal is impossible or where malignant degeneration has occurred.

Sympathectomy.—BARDON and MATHEY-CORNAT (*Lyon. chir.*, 1923, 20, 694) say that the periarterial sympathectomy is a new method for curing varicose veins in leg and foot. Several case reports are appended. The immediate results, and late findings are satisfactory. Contraindications for this radical treatment are extremely advanced sclerosis with arteriomalacia, decompensated cardiopathies, renal and hepatic insufficiency. The technic moreover is exacting. Results are not obtained in insufficient decortication, while perforation of the artery calls for ligation.

Treatise on the Interureteral Bar.—BLANC (*Jour. d'urol. med. et chir.* 1923, 4, 274) declares that clinical observations upon this subject are rare. Pasquereau, Deton, Caulk and Young have been the more thorough observers. It is by definition a salient part of the trigone, extending transversely between the two ureteral orifices dividing the vesicle cavity into two parts, and a definite factor in dysuria, and retention of urine, complete or incomplete. It is found only in the human bladder. Young has found it pronounced in cases presenting mal-

formation, such as hydrocephalus and spina bifida. The diagnosis of disturbance at this site is by positive urinary signs in absence of prostatic pathology. Use of cystoscopic examination and catheter passage are important signs in differential diagnosis from prostatic hypertrophy.

The Incidence of Malignant Disease in the Apparently Benign Enlargement of the Prostate.—SWAN (*Lancet*, 1923, 205, 971) states that Wade of Edinburgh, in 1914, found 14 carcinomatous prostates in a series of 134 specimens of enlarged prostates. Of these 10 were removed at operation and were assumed to be benign tumors. Malignancy was only found at microscopical examination. Walker, in 1922, found 16 cases showing localized carcinoma of a consecutive 100 specimens removed for simple hypertrophy. The average percentage of malignancy present in apparently benign prostatic enlargement in three consecutive series was 12.9 per cent. The author draws analogy between these cases and those of carcinoma in other glandular structures of the body. In the breast, tongue, stomach and intestine the opinion has been expressed that carcinoma may occur in areas which have been the seat of simple chronic inflammation or of ulceration.

Roentgenography of Urinary Tract During Excretion of Sodium Iodide.—SUTHERLAND and ROUNTREE (*Jour. Am. Med. Assn.*, 1923, 80, 368) state that it is possible to obtain roentgenograms of the urinary tract during the excretion of sodium iodide following its intravenous or oral administration. The method uniformly gives excellent and accurate shadows of the urinary bladder, and renders reliable information relative to its size, shape and location. It has been partially successful in depicting the renal pelves and the ureters in a limited number of cases. In a number of cases, it assists in revealing the kidney itself through intensifying the renal shadow. It has been proved a success in revealing the existence of residual urine in the bladder, and in furnishing approximate information of the amount; thus eliminating the necessity of catheterization, and its attendant dangers of infection.

The New Type of High-voltage Roentgen-ray Therapy in the Treatment of Carcinoma of the Bladder.—WATERS (*Am. Jour. Roentgenol.*, 1924, 11, 19) says that the introduction of the cystoscope brought the first successful efforts in handling bladder tumors, mainly on account of the increased possibilities of earlier diagnosis. Fully 50 per cent of the tumors could be successfully removed or destroyed by operative procedures. The tendency for recurrence in other parts of the bladder was noticed. Repeated suprapubic operations were out of the question. Moreover, relatively benign growths became extremely malignant. Fulguration, introduced in 1910, showed that the so-called benign and malignant papillomata could be successfully handled by this intravesical method. The procedure, however, is worse than useless in the treatment of papillary carcinoma either superficial or infiltrating. Experience with radium has shown that superficial papillary carcinomas comprising 15 per cent of the bladder tumors seen, could be dealt with successfully. Twenty-five per cent of the tumors by location and extent cannot be successfully handled. Deep roentgen-ray therapy

can be said to have a very definite and specific influence in certain types of carcinomas of the bladder. Experience will probably show that it has a marked influence on the multiple superficial papillary carcinomas which reappear under radium almost as fast as they are removed. Moreover, a combination of deep therapy and radium will work results that neither method alone would effect for permanent results.

Internal Derangements of the Knee-joint.—CLAYTON (*Texas State Jour. Med.*, 1923, 19, 446) says that internal derangements of the knee-joint, though a common source of disability have received scant attention. The commonest type of derangement is that in which the internal semilunar cartilage is torn. In properly selected cases the results of removal of the cartilage are excellent. Operation should not be done for torn cartilage unless reduction is impossible following locking or unless locking has been repeated. Traumatic synovitis, sprains of internal lateral ligament, hypertrophy of the post-patellar fat, bad rupture of the crucial ligaments, fracture of the tibial spine and loose bodies are other causes for internal derangements. The knee joint is as tolerant of infection as is the abdomen though infections in the joint are serious. A wasted quadriceps muscle should be redeveloped by massage and exercise after operations for knee-joint derangement.

Benign Bone Cysts.—BLOODGOOD (*Jour. Radiol.*, 1923, 4, 345) states that no cause is known for this lesion. Clinically benign, it is pathologically a form of chronic inflammation. The author treats of the non-operative treatment, especially where spontaneous fractures have occurred. The operative method is the crushing of the bone shell. He does, however, emphasize the fact that in a small number of bone cysts, left alone there may be no ossification or very little, with consequent growths of the cyst to great size, when it not only interferes with function, but makes the operation to restore the bone to normal dangerous and in some instances impossible. The patient should be followed carefully with frequent roentgen-ray examinations, so that operation can be resorted to the moment it is indicated. The operation is essentially a comminuted fracture when performed intelligently.

The Endotracheal Administration of Nitrous-Oxide-Oxygen-Ethanol as the Routine (an Anesthetic of Choice for Major Surgery).—HEWER (*Brit. Jour. Anaesthesia*, 1924, 3, 113) says that it is probably the safest known method of anesthesia, whether general, local or combined. It is the only method of complete muscular relaxation or suspension of respiration that can be performed safely. It is of universal advantage in operations upon stomach, gall-bladder or lung where suturing is greatly facilitated. It is the only safe method in extensive thoracostomies in which both pleural cavities may be opened simultaneously, necessitating continuous inflation of the lungs. The technic is described in detail with outlines and photographs of apparatus. The disadvantages are outlined as follows: A heavy and complicated apparatus is necessary; expense is marked; considerable experience is necessary before the anesthetist can be certain of introducing the catheter into the trachea quickly.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK.

"Hexeton," an Isomeric Compound of Camphor for Hypodermic Use, Soluble in Water.—GOTTLIEB and SCHULEMANN (*Deutsch. med. Wchnschr.*, 1923, 51, 1533) report an isomeric compound of camphor, hexeton (F. Bayer & Co.) which is soluble in an aqueous solution of sodium salicylate and is stable, sterile, and suitable for intravenous or intramuscular injection. For subcutaneous or intramuscular use 1.5 to 2 cc of a 10 per cent solution of hexeton in a 25 per cent solution of sodium salicylate is given; for intravenous use 1 cc of a 1 per cent solution. The pharmacological action of hexeton is the same as camphor, but it is two to four times as active, and because of its solubility, its action is much quicker than that of the oily solutions of camphor. Hexeton is eliminated in combination with glycuronic acid in the urine. The clinical use of hexeton is reported by KREHL and FRANZ. (*ibid*, p. 1535) who used it in cases of shock and collapse or whenever a respiratory stimulant was indicated. After intravenous injection the maximum effect was obtained in two to fifteen minutes, and after intramuscular injection the first effect was noted in three to ten minutes. They conclude that intravenous injection has scarcely any advantage over intramuscular injection. In 90 per cent of the cases the pulse increased five to fifteen beats a minute; the blood-pressure remained unchanged or rose from 5 to 10 mm. of mercury. Respiration was more greatly influenced by hexeton than by camphor. No harmful or toxic effects were noted.

The Neosalvarsan Treatment of Gangrene of the Lung.—VON WINTERFELD (*Therap. d. Gegenw.*, 1923, 11, 415) advocates the use of neosalvarsan intravenously in the treatment of gangrene of the lung whether spirochetes and fusiform bacilli are present as the exciting agents or not. He reports 2 more cases cured by neosalvarsan injections at the end of a few weeks' treatment, and 1 case was complicated by nephrosis. The initial injection given was 0.15 gm. neosalvarsan and thereafter 0.3 gm. every fourth day until 6 injections in all have been administered.

The Nature and Treatment of Sprue.—SCOTT (*Brit. Med. Jour.*, December, 1923, p. 1135) found a reduction in the ionic calcium content of the blood in cases of sprue, and from this deduced a new theory and offers a new treatment. Because of the relative excess of fatty acids in the stools, and the large calcium output in stool and urine he was led to believe that there was a disturbance in the metabolism of calcium. Analysis of the blood of these patients confirmed this opinion, and he states, "In cases of sprue we have one of two conditions. In

the one where fats are in excess we have an excessive excretion of calcium in addition to intoxication of intestinal origin; in the other protein excess with intestinal toxin formation. In both, the parathyroid detoxicating function is overburdened, with a resultant disorganization of its calcium regulating function, while in addition there may be diminished calcium absorption. Both functions, therefore, of these glands are interfered with." By the administration of parathyroid and calcium lactate he has had excellent results, some of his cases having been cured in five or six weeks. He calls attention to the fact that the best diet and the most successful drugs used in the treatment of sprue contain an abundance of calcium and believes that the regulating function of the parathyroids is at fault.

Acute Lumbago Treated by the Injection of Quinine and Urea.
—SOUTTAR (*Brit. Med. Jour.*, November, 1923, p. 915) reports relief of pain followed by complete cure of acute lumbago by the injection of a local anesthetic into the point of greatest tenderness. He uses a 1 per cent aqueous solution of quinine and urea hydrochloride as the local anesthetic and injects 5 cc of this solution into the deep tissues. Within ten minutes after injection the acute pain ceases, and the anesthesia may last for three days, at the end of which time there is no return of pain or loss of function.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Blood-pressure in the Newborn.—RUCKER and CONNELL (*Am. Jour. Dis. Child.*, 1924, 27, 6) in their observations used the arm entirely for the taking of the blood-pressure. They made an arm band by sewing a Barnes bag 4 cm. wide between two layers of sateen in imitation of the arm band supplied with certain sphygmomanometers. It was found that it was not practicable to make a graphic record, but the needle of the sphygmomanometer showed the pulsations plainly. It is quite important that the babies be quiet, as muscular contractions of the arm obscure the pulsations of the artery. Any effort to hold the arm still is resisted, and this makes it difficult to obtain an auscultatory reading. The arm band was adjusted to the arm and the baby was covered with a blanket. If the infant did not become quiet in a few moments, he was given a bottle of sterile water. This usually quieted him. The readings were repeated several times, and whenever possible were also made by the auscultatory method. The first distinct pulsation of the needle was taken to indicate the systolic pressure, and the point at which the amplitude of the pulsations diminished, the diastolic pressure. The mean systolic pressure was found to be 55 mm. of

mercury at birth. The mean diastolic pressure was found to be 40. The systolic pressure increased with the age of the infant more rapidly than did the diastolic pressure. Toxic conditions of the mother seemed to have some influence on the blood-pressure of the child and this was more marked on the first day of life. This method may possibly furnish an additional sign of some value in the diagnosis of intracranial hemorrhage. The blood-pressure in general varied directly with the total length of the infant. Sex showed no influence on the blood-pressure, and there was no difference in the blood-pressure of the white and the colored babies.

Treatment of Early Hereditary Syphilis with Intramuscular Injections of Sulpharsphenamine.—BOONE and WEECH (*Am. Jour. Dis. Child.*, 1924, 27, 39) found that sulpharsphenamine is a safe and easily administered arsenical preparation for the treatment of hereditary syphilis in infants. This remedy can be safely given to infants in a dose as large as 20 mg. per kilogram of body weight. The reactions, general or local, are very slight. In 55 per cent of the patients the Wassermann reaction became negative after one course of six treatments. The symptoms of hereditary syphilis rapidly disappear, and the patient's general condition quickly improves after treatment. Because of the ease with which sulpharsphenamine can be administered, it should be very useful to the practitioner who is not adept at intravenous therapy. In the series of cases reported the injections were given at weekly intervals. The patients were then allowed a rest period of two months before a second course was started. During this interval mercury inunctions were given. A portion of one-third strength blue ointment about the size of a pea was applied each morning on a flannel abdominal band. The exertion of the infant crying, kicking and the like furnished the friction necessary for absorption. Three full courses of the sulpharsphenamine were given after the Wassermann was negative, making a minimum of four courses in all. The drug was given intravenously, subcutaneously and intramuscularly. The muscles of the buttocks seemed to be the best place of injecting the drug. If care is taken in expelling all of the drug into the muscle from the needle before withdrawing the needle, there is little likelihood of reaction occurring.

The Value of the Low Fluid Content of the Butter-flour Mixture.—GREENWALD (*Arch. Pediat.*, 1923, 40, 812) points out the indications for the use of butter-flour mixture. It may be used as artificial nourishment for the normal healthy infant, giving a total fluid quantity not in excess of that taken by a breast-fed child. It may be used in children with manifestations of exudative diathesis such as eczema, recurrent nasopharyngitis, chronic bronchitis and recurrent rhinitis. It may be used for premature infants who must have an artificial diet. It may be fed to atrophic infants. It may be used in spasmophilia. It may be used in the reparation period following acute diarrheal disturbances, particularly where a soap-stool formation is desired. The contraindications may be summed up in a few words. It should never be employed for infants suffering from acute nutritional disturbances as manifested by diarrhea, marked loss of weight and fever. It should be discarded if the infant reacts to it by a loss of weight. It must be

remembered that some infants have an unusually low tolerance for fat of any kind and when such babies are under treatment, the mixture must be reduced in amount or wholly withdrawn, if severe disturbances manifest themselves. The mixture is a food that is simply and easily prepared. With its use the artificially-fed infant is satisfied by a fluid bulk not exceeding that normally ingested by breast-fed infants. It permits the employment of fat, an important factor in the economy of the child, without the manifestations of such disturbances as are frequently observed in the use of ordinary fat enriched mixtures. In the butter-flour mixture, we have a food that in quantity, and in the correlation of fat, protein and carbohydrate to one another, more nearly simulates breast milk than any other mixture heretofore employed.

A. Skin Test for Susceptibility to Scarlet Fever.—DICK and DICK (*Jour. Am. Med. Assn.*, 1924, 82, 265) used 0.1 cc of a 1:1000 dilution of filtrate from streptococcus hemolyticus with which experimental scarlet fever had been produced. This was injected into the skin of the forearm. The small swelling which resulted disappeared in a few minutes. The positive reactions usually began to appear from four to six hours after the inoculation. At first there was a small circular area of erythema. This red area increased until the maximum was reached, between eighteen and thirty-six hours after the injection. The reddening was usually associated with some swelling of the skin. In the most strongly positive tests, the reddened area continued to spread, and the swelling increased up to about thirty-six hours after the inoculation. Soon after reaching the maximum the reactions began to subside. Even the most strongly positive reactions did not persist more than forty-eight hours. The bright red color became dull and began to fade. The swelling disappeared. There was left only a faintly yellowish area. This sometimes desquamated during the week or ten days following the test. The reactions were observed at the termination of twenty-four hours and were classified as negative, slightly positive, positive and strongly positive. Those designated as negative showed only by the point of the needle prick or by a faint pink streak along the course of the needle in the skin. Slightly positive reactions consisted of a faint red area less than 2 cm. in diameter, without swelling of the skin and without tenderness. Positive reactions were from 1.5 to 3 cm. in one or both diameters, and bright red with some swelling of the skin, and occasionally slight tenderness. Strongly positive reactions were more than 3 cm. in one or both diameters and intensely red, with marked swelling of the skin, and usually some tenderness. Those strongly positive reactions were often from 5 to 7 cm. in diameter. The swelling showed a sharply raised edge, and extended beyond the reddened area. Positive or strongly positive reactions were obtained in 41.6 per cent of the persons who had no history of scarlet fever. All of the convalescent scarlet-fever patients tested showed negative or only slightly positive reactions. The action of the filtrate on the skin was inhibited by convalescent scarlet-fever serum mixed with the filtrate before it was injected or given intramuscularly before the test was made. In two instances in which it was possible to observe the test before and after an attack of scarlet fever, it was positive before the attack and negative after the attack during convalescence.

Children's Upper Respiratory Abscesses Descending into the Neck and Mediastinum.—GLOGAU (*Arch. Pediat.*, 1923, 40, 801) says that in childhood, abscesses in the upper respiratory and alimentary tracts occur frequently, and may easily descend by way of the regional lymph vessels and glands into the parapharyngeal, retropharyngeal, and retroesophageal loose connective-tissue spaces, causing phlegmon of the neck, and descending alongside the vascular sheath into the mediastinum, causing mediastinitis, sepsis and death. Conservative treatment, including local incision, may be tried. With the swelling of the neck increasing in size, and becoming more tender and discolored, with the occurrence of pains in the region of the jugulum and the appearance of severe general symptoms, the typical external operation should be resorted to. It consists of a wide exposure of the vascular sheath, and of the direct opening and draining from there of the parapharyngeal, retropharyngeal and retroesophageal spaces. These deep descending abscesses frequently are complicated by suppurating glands intimately connected with the jugular vein, which by itself may be flask-like distended. These glands can hardly be reached by simple incision from without or within, without endangering the life of the child by puncturing the large vessels, especially the distended jugular vein. In severe cases, where mediastinitis is threatening or present, the anterior and posterior collar mediastinum is exposed. It is sealed with iodoform gauze if found to be still healthy and is drained if diseased. Even in the absence of pus, where the descending infection expresses itself by widespread and spreading edema and infiltration, the exposure of the vascular sheath and the wide opening of the loose connective-tissue spaces of the neck, combined with prophylactic collar mediastinotomy, appears to be the only logical method. When resorted to early, the typical external operation is a life-saving procedure in upper respiratory abscesses descending into the neck and mediastinum.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Arsenic in the Nervous System in Treated Neurosyphilis.—CORNWALL and MYERS (*Am. Jour. Syph.*, 1923, 6, 629) reach the following conclusion: (1) There is a significant difference in the chemical physiology of arsenic in the various types of neurosyphilis. (2) When the lesions are essentially confined to the mesodermal structures arsenic can be detected in 80 to 100 per cent of fluid, as compared with 60 to 90 per cent when the ectodermal tissues are involved. (3) In mesodermal syphilis quantitative determinations can be made in 67 to 94 per cent of fluids, as compared with 40 to 87 per cent in ectodermal

syphilis. (4) The average quantity of arsenic in the spinal fluid in mesodermal syphilis is 14 to 17 mg. per cent; in ectodermal, 4 to 9 mg. per cent. (5) In mesodermal syphilis the quantity of arsenic in the spinal fluid is greatest at intervals of two and seventy-two hours after intravenous administration of silver arsphenamine, the average amount after seventy-two hours being slightly in excess of that found after two hours. (6) In ectodermal neurosyphilis the largest amount is present two hours after intravenous administration, diminishing at subsequent periods.

Experimental Studies of Syphilitic Leukoderma.—EHRMAN and WERTHEIM (*Arch. f. Dermat. u. Syph.*, 1923, 142, 129) experimented with the production of syphilitic leukoderma in patients with syphilitic eruptions by ultraviolet-light irradiation, with a view to studying the mechanism of development of this valuable diagnostic sign. They found that there is an abortive type of leukoderma which runs a very brief course and disappears in a few weeks, though the clinically familiar type persists for months. Leukoderma syphiliticum only appears where a mild exposure to actinic rays has occurred. It only develops where there has been a macular or papular eruption, and each fleck of depigmentation occurs at the site of a previous macule or papule. The lesion may be so insignificant that it barely comes to clinical recognition, and can only be detected by microscopical search. The effect of actinic exposure is not to produce the leukoderma, but to render it recognizable by pigmenting the unaffected parts of the skin to produce contrast. There is not the slightest evidence that syphilis produces the pigmentation observed with the lesion. Leukoderma syphiliticum accordingly develops by predilection upon those sites which are normally exposed to actinic light, especially the necks and shoulders of women. The pathological mechanism is apparently a diminution in the functional activity of the pigment-producing basal cell of the epidermis in the presence of the *Spirocheta pallida*. Sharp stimulation may overcome this diminished functional activity in the leukodermatous patient, or, as is usually the case, the affected pigment cells in the leukodermatous area recover their function spontaneously and the skin returns in time to its normal pigmentation.

Gastro-intestinal Findings in Adult Eczema and their Significance for a Rational Therapeutic Management.—URBACH (*Arch. f. Dermat. u. Syph.*, 1923, 142, 29) discusses the observations made in Ehrmann's Clinic on the clinical pathology of the gastro-intestinal tract in eczema. In 32 cases of neurodermatitis 10 had complete achlorhydria, 13 showed a marked and 6 a moderate reduction in free HCl. In only 4 patients was the acidity normal. In two-thirds of the patients the quantity of gastric secretion was increased. Microscopical findings included many Oppler-Boas bacilli. Roentgenologically, 13 patients showed hypersecretion, 5 hyperperistalsis, 7 hypermotility, 8 ptotically elongated stomach, 5 atony, 3 hypotonia and 1 "cascade stomach." The hypersecretion is attributed to a dilute gastric juice. Roentgenologically, the intestinal tract showed enlargement of the sigmoid associated with clinically severe constipation and redundancy of the transverse colon. The gastro-intestinal symptoms indicate

functional abnormality of the gastro-intestinal tract in a number of cases in which no abnormality was demonstrable roentgenologically. In discussing the bearing of these findings on treatment, the author recalls the observations of Schmidt on the association of eczema, anacidity or subacidity and bradycardia, and of Bertelli, Falta and Schweeger on temporary lymphocytosis and eosinophilia in patients with sympatheticotonia. In 6 patients in the present group, whose blood was examined, a monocytosis and eosinophilia was observed 5 and 4 times respectively. Treatment is directed less toward the comparatively easy immediate end of clearing up the dermatitis, and more toward the more difficult objective of preventing relapse. The general condition of the patient is improved by obviously needed surgical interventions, such as removal of chronically inflamed appendices, and by the destruction of intestinal parasites. If there is evidence of a true gastritis, as distinguished from merely functional disturbance, the cause is sought in chronic alcoholism, chronic nasal infections, bad eating habits, especially imperfect mastication and haste at meals, and clinical tuberculosis. In functional anacidity a diet adapted to gastric hypermotility is prescribed, including small frequent meals and small fluid intake; coarse foods with a high cellulose content are interdicted. In subacidities, dilute HCl is given by mouth in 10-drop doses one hour before meals. In achylia of long standing the needed acid and pepsin must be supplied over a considerable period. Rest in bed and changes of scene are helpful in these cases. Occasionally a paradoxical intolerance of HCl treatment is seen in patients of this type, and in them alkali may be helpful. When there is evidence of pancreatic deficiency pancreatic ferment (pancreon) is administered with pepsin and HCl. Hypersecretion is managed by the use of the finely divided meal and avoiding of seasoned or irritating foods, such as coffee, bouillon and condiments, with reduction in fats, cream, butter. In hypermotility HCl is helpful, and in atony and ptosis finely divided meats and pea puree are used empirically. The benefits of these systemic régimes are apparent in a marked improvement of the general health and prolonged freedom from relapses which cannot be obtained by merely local measures.

The Etiology of Scleroderma.—CASTLE (*Brit. Jour. Dermat.*, 1923, 35, 303) reviews the literature on the etiology of scleroderma in the light of 12 cases in his own experience. Scleroderma is found more often in association with thyroid disorder than with disturbance of any other endocrine gland. Trauma and irritation, shock, heat, infectious disease, disorder of the mesenteric glands, congenital factors, pregnancy and syphilis are all dismissed as not directly responsible. The theory of a nervous origin for scleroderma has more supporters than any other. The author believes, from his review and observations, that the essential cause of scleroderma is a combination of disordered function of the internal secretory glands with an affection of the central nervous system. He feels that the glandular mechanism acts as a whole, and that the compensation of one element for another which may be in a state of dysfunction explains the variable clinical picture in different cases. Nervous strain or long-continued poisoning from dental, intestinal or tonsillar sepsis is held to be a leading factor in the endocrine failure.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Injury to the Fetal Cranium and Spinal Column Occurring during Labor.—Two interesting and valuable papers (*Surg., Gynec. and Obst.*, December, 1923, pp. 790 and 802) are published upon this subject. The first is by CROTHERS, with the title "Changes of Pressure Inside the Fetal Craniovertebral Cavity." He believes that successful childbirth depends very largely upon the preservation of barriers which prevent pressure upon the fetus from injuring the central nervous system. In these cases there was no serious disproportion between the size of the fetus and the pelvis; mother and child were in good condition and the presentation was either vertex or breech. When asphyxia is present it is commonly believed that pressure on the fetus, irritating the vagus nerve, may slow the action of the heart and also that respiration may be hindered by the presence of amniotic liquid or mucus in the child's mouth and throat. The writer believes that the viability of the fetus depends upon the integrity of the cells of the medulla and upper cord. If this be true the fetus can survive for at least twenty minutes without breathing. During labor pressure is exerted upon the child by the contraction of the uterine muscle. If delay occurs the pressure of the uterus is often reinforced by artificial aid; thus the forceps increases pressure. Breech presentation is also dangerous. Direct pressure upon the fetal head occurs at the moment of delivery, with traction upon the legs or body of the child. This is unusual and unnatural, for the fetal tissues are ordinarily subjected to compression only. The fetal cranium has two divisions: The base of the cranium is rigid and is not readily compressed; the vault is formed by flexible plates of bones loosely bound together. The intracranial cavity is divided into three by dural septa. The cerebral hemispheres are partially separated by the falx extending from the ethmoid to the median line of the tentorium. This latter arises at the junction of the bones forming the vault of the cranium and extends to the midline of the tentorium. These membranes carry bloodvessels, protect the brain from tension and pressure and control intracranial pressure. The spinal column of the child can be altered about 2 inches by stretching or compression of the fetus between the hands of the observer. The spinal dura is adherent in the cervical and lumbar regions, while the cavities above the tentorium are compressible to a marked degree. The space below the tentorium is small and almost fixed in size and shape. No great change in its capacity can occur without rupture of surrounding tissues. When the effects of force applied to the fetus during labor are studied two injuries are most often found: One is rupture of the falx cerebri or of the tentorium and the other is rupture of the cervical spinal column. While these lesions in themselves are not fatal, they expose the medulla and the

upper cord to injury. In ordinary conditions the medulla is protected from pressure by the tentorium and also the balance of fluid pressure at the foramen magnum which prevents downward dislocation of the contents of the posterior cranial fossa. When injury occurs this balance of pressure is destroyed and the effect of pressure is conveyed directly to the nervous tissues. In breech extraction, rupture of the tentorium occurs in 88 per cent of still-births following normal breech labors. A considerable number of injuries to the spine and spinal cord result from traction during breech delivery. Methods of producing artificial respiration may injure the brain or cord of the newborn and terminate fatally. We have no clearly defined description of the pathology of asphyxia. Autopsies show that efforts to resuscitate the child often cause more injury than the original asphyxia. PIERSON writes concerning "Spinal and Cranial Injuries of the Baby in Breech Deliveries," quoting observations made at the Sloane Maternity. Birth injury and shock in breech deliveries cause greater fetal mortality and morbidity than does asphyxia alone. It is especially important that unnecessary haste be avoided in performing breech extraction. From eight to twenty-three minutes may be occupied in this manipulation without damage to the infant. It is impossible to make a positive diagnosis of death from asphyxia in breech delivery unless it can be shown by autopsy that injury in birth is absent. In view of the danger to the child in breech delivery, it should be avoided by performing external version when possible and by limiting strictly the indications for version and breech extraction. Better results may be obtained in breech deliveries by securing full dilatation before delivery. During extraction fetal diameters should be brought in relation to those of the pelvis in such a way that difficult and dangerous traction are avoided.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Leukoplakic Vulvitis.—Having observed 40 cases of this disease, TAUSSIG (*Am. Jour. Obst. and Gynec.*, 1923, 6, 407) states that the term kraurosis, which is frequently applied to this condition, is merely a symptom of the disease and not a disease in itself. If we use the term at all, it should be limited to that simple form of atrophic vulvitis resembling in its pathology and course atrophic vaginitis which is unattended by leukoplakic changes. He prefers to call this condition atrophy sclerosis of the vulva, and so eliminate the ambiguity that still clings to the term kraurosis. Sixty per cent of the women in this

series were over sixty years old, while of the 6 who were under forty, 4 merely had patches of leukoplastic vulvitis and 1 was an artificial menopause after a hysterectomy. There was only 1 case of the 40 in which a typical complete leukoplakic vulvitis developed in a woman before the menopause period. All but 9 of the women had had one or more children, 5 of them were nullipara and 4 were virgins. In only 1 patient was pruritus absent and in a few others it was only mild, but as a rule, it was constant and unbearably severe. Although leukoplakic vulvitis is a slowly progressive disease, Taussig distinguishes three stages, merging one with the other. In the first stage the vulva assumes a swollen reddened appearance, at times having a moist surface and showing here and there whitish or pinkish-white areas. Microscopically at this time there is pronounced acanthosis with slight increase in the keratin layer of the epidermis while in the connective tissue there is marked round-cell infiltration with occasional leukocytes especially in the papillary spaces. In the second stage of the disease, appearing usually not until about one year has elapsed there is a markedly thickened, white skin with stiff edges and often excoriated from scratching. The acanthosis is still marked but there is also a piling up of the keratin layer and a thick deeply staining layer of eleidin cells. The connective tissue shows the picture of chronic inflammation with here and there a collagenous appearance and numerous plasma cells are present. In the third stage the skin has assumed the appearance of thin parchment, pearly white, crackled and dry. The epithelial layer is low, papillary processes are absent, the keratin layer usually a half or a third as thick as before, the eleidin cells less numerous and a peculiar frayed-out appearance of the basal cells of the epidermis. In the connective tissue there is a glairy looking collagenous material replacing the connective tissue, with here and there islands of round-cell infiltration. Characteristic of all three stages is the absence of elastic tissue in the subepithelial layers of the dermis which becomes increasingly marked as the disease progresses. It is this absence of elastic tissue, according to Taussig, which is primarily responsible for the disease. His explanation of the etiology is that in some women at or after the menopause there occurs a complete disappearance of elastic tissue in the upper layers of the vulvar skin about the introitus which leads to greater friability so that minute breaks of continuity readily occur. Through such cracks bacteria gain entrance to the dermis and produce a low-grade inflammation. The exudate thus resulting produces pruritis, which, in turn, through the traumatism of rubbing or scratching, produces more cracks and more infection, so that the vicious circle progresses until the characteristic changes above described have been produced. Cancer may develop at any of the three stages, but is most frequent and most malignant when it originates in the second stage, that of epithelial hypertrophy. In the third stage, if a cancer appears it is often evrting in type, slow in growth and runs a relatively benign course.

Treatment of Chronic Leucorrhea.—Probably the most frequent complaint which the gynecologist is called upon to relieve is the annoying discharge characteristic of chronic leucorrhea and it is not to the credit of the profession that the results of our treatment have been far from satisfactory. The most interesting and scientific investigation

of this subject in recent years has been done by CURTIS (*Surg. Gynec. and Obst.*, 1923, 37, 657) who admits that his treatment prior to 1919 yielded distinctly disappointing results. Since that time 140 patients have been treated, not including a very considerable number in whom office management has been sufficient to afford relief. Only the most severe and most chronic cases, all subjected to a trip to the hospital are here considered. In these cases the patient is given nitrous oxide anesthesia and the vicinity of the urethra is searched for infected Skene's ducts and urethral glands. Diseased foci are threaded on the blunt end of a needle, the tract laid open with a knife, and the lining fulgurated or otherwise cauterized. Cure of the diseased cervix may be achieved through radium application, which produces atrophy of the infected glands, or through removal of the endocervix. Surgical removal, according to the method of Sturmdorf, has yielded excellent results in those selected cases in which it has been employed. In Curtis' work radium is given preference in patients with evidence of infection extending high into the cervical canal, in those with strictures in the vicinity of the internal os, in patients with profuse, creamy discharge, in those whose cervix is inaccessible to surgery, and in instances where removal of the diseased tissues promises to require extensive or difficult operation. Wedge-shaped excision of the anterior lip, or other simply performed removal of diseased tissue, is often combined with the radium application. The fundamental requirement is that the patient be relieved of the diseased, discharge-producing tissues; further experience will best determine whether a given patient shall be treated with radium or subjected to removal of the endocervix. The technic of radium treatment is as follows: The cervical canal is investigated with graduated dilators. Thorough dilatation is made without producing laceration. Diagnostic curettage, separate for cervix and fundus, may be desired. Two 25 mg. tubes of radium, in tandem, are introduced into the cervix and held in position by a Michel clip at the external os. The screen now used is a rubber-covered gold capsule, 0.5 mm. in thickness. Young women with regular menstruation receive application for seven hours; treatment for this period of time never disturbs the menstruation. Patients over thirty-five years of age must be treated with greater caution. The immediate result of radium treatment is increased discharge, which persists for many weeks. This stage is often followed by a stationary period of a month, or even two months. Meantime, the cervix should be dilated occasionally to prevent stenosis. This can be done in the office. Gradual improvement is the rule; recovery after a single application is frequent, but a considerable number require a second radium treatment to effect a thorough cure. This is preferably postponed for several months, first, because one treatment may eventually prove to be sufficient, second, because it is desired to ascertain with certainty that radium has not interfered with the menstrual function. The dosage of the second application varies with requirements, but may almost always equal the amount first used, if desired. At this time, attention should again be directed to Skene's ducts, which may not have been completely destroyed at the first treatment. It should be particularly emphasized that several patients with long-standing leucorrhea, in whom the results of treatment appeared unsatisfactory, upon return nine months or one year later revealed absolute recovery from their affliction.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

Pathogenesis of Experimental Pneumonia in the Rabbit.—PERMAR (*Jour. Med. Res.*, 1923, 44, 1) has recently reported an investigation of experimental pneumococcus pneumonia in the rabbit, in which 2 series of animals (27 in all) were subjected to the instillation, under ether anesthesia, of a small quantity of fresh pneumococcus culture into the upper end of the trachea. An acute pneumonia developed in 19 instances. The animals were killed at stated periods, the plan being to study the effects of the injected organisms at very frequent intervals in the earliest hours, and at fairly frequent intervals up to seventy-two hours. The results were not entirely in agreement with some of the recent work along similar lines. The author concluded from his study of the progressive stages of the experimental lesions that the mode of invasion was by direct extension over the surface of the air passages, and therefore definitely by the aërogenic route. No evidence of primary lymphatic invasion and dissemination by either the tracheal or bronchial lymphatics was found in any instance, though the entire larynx, trachea and lung were particularly searched for this reaction. The respiratory tract throughout its extent was shown to be involved simultaneously after an intralaryngeal instillation; but the lesions were not uniformly severe. The most active response was found in the delicate air spaces and in the terminal bronchioles. This primary acute bronchitis and bronchopneumonia was followed in about ten hours by the appearance of acute interstitial inflammation. And this aided in completing the consolidation of affected lobes and at the same time led to the development of complications such as pleuritis, pericarditis, mediastinitis, arteritis and septicemia. The latter appeared as early as ten or twelve hours in both series. The organisms were recovered from the blood and identified as *Pneumococcus* Type I in 11 of the 19 animals with pneumonia.

The Mononuclear Phagocytes in Experimental Pneumonia.—A companion study to the foregoing, by the same author, PERMAR (*Jour. Med. Res.*, 1923, 44, 27), was based on the findings in the second group of experimental pneumonias, in which vital staining by the India-ink method of McJunkin and Foot was performed just prior to, and subsequent to the instillation of the pneumococcus culture. The first (unstained) group of experimental pneumonias served as controls for this series. The vital staining had no apparent effect on the course of the lesions and offered an opportunity to study the large mononuclear

phagocytic cells of the acute pneumonic exudate. This cell group, the author points out, is not confined to the later stages of the inflammatory reaction but may be quite prominent early in the disease. As a result of the use of the India-ink method in this work, it has been possible to demonstrate the origin of these phagocytes from vascular endothelium, probably in large part from the local capillary endothelium in the affected portions of the lung. These cells, then, were shown to belong to Mallory's group of endothelial leukocytes. Further, the author states that in these studies there was no evidence to support the older view which interpreted the alveolar phagocytes as derived from the alveolar epithelium. The findings are in agreement with other recent studies of this phase of lung cytology.

The Effect of Suprarenalectomy in Rabbits on Hemolysin Formation.—"The active participation of the suprarenal cortex or interrenal gland in the defensive mechanism of the body, particularly against intoxications and infectious diseases, has long been suspected by pathologists. Hyperemia, edema, hemorrhage and focal necrosis occur particularly in cases of food poisoning, skin burns and acute infections. Examination with polarized light has shown that the anisotropic 'lipoids' greatly decrease during acute infectious diseases and chemical examination of the interrenal gland has shown that the 'lipoid' loss consists mainly of cholesterol and its esters. From these facts, the view that the interrenal gland is concerned directly or indirectly with the neutralization of toxins arose." Inasmuch as this view has received experimental support, TAKÉ and MARINE (*Jour. Infect. Dis.*, 1923, 33, 217) conducted a series of experiments, to note the influence of suprarenalectomy in rabbits on hemolysin formation. Double suprarenalectomy was accomplished in two stages on male and female rabbits. Of the 31 rabbits operated upon, 11 died within the first three weeks after removal of the second suprarenal. The remaining 20 rabbits were injected every second day with a 50 per cent suspension of sheep cells, intravenously, in ascending doses, ending with 20 cc. Six of these rabbits died from the direct toxic effects of the antigen. Natural antisheep hemolysin was determined before injections were instituted and 30 control rabbits were used. Titrations were made every third day after the last injection, using 0.05 cc inactivated serum, 2 units of complement and 0.1 cc of a 5 per cent suspension of sheep cells. It was found that the hemolysin titers in the suprarenalectomized rabbits averaged more than twice as high as in the control rabbits. The authors believe that "the increased antibody formation is due to the loss of some regulatory and inhibitory influence which the interrenal gland normally exerts on the irritability and susceptibility of the body cells" and that "this influence may involve physical and chemical alteration in their lipid mechanism."

Studies on the Peritoneal Fluid in Anaphylactic Shock.—By sensitizing guinea-pigs to egg white and reinjecting them intraperitoneally after three weeks or more and determining the freezing point of the blood serum, FLEISHER and MAYER (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 26) found higher readings in the shocked animals than in the normal animals, thereby differing from the findings of Segale who

reported a marked fall of the freezing point of guinea-pig serum during shock. In addition, normal and sensitized animals were inoculated, intraperitoneally, with 6 cc of a 50 per cent egg white and 30 cc of sodium chloride solution. Freezing-point determinations, made at varying intervals, of the fluid in the abdominal cavity, showed a lowering of the freezing point in the shocked animals, a lowering which was not momentary but gradually tapered off over a two-hour period. The authors believe it is possible that this difference in freezing point might be due to a difference in the absorption of the sodium chloride in the two series of animals and that the experiments give direct evidence that in anaphylactic shock the permeability of cells or cell membranes is definitely affected, although they cannot state whether this change is in relation to organic or inorganic substance, to crystalloids or to colloids.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. MCCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Pellagra Prevention by Diet among Institutional Inmates.—GOLDBERGER (*Pub. Health Reports*, 1923, 38, 2361) after reviewing the work, discusses the subject in the following terms: It appears, then, that at each institution at which the test was made, barring cases admitted as such during the progress of the test, pellagra promptly disappeared. And it is perhaps important to note that this was not merely a marked reduction in prevalence, but in each instance a complete disappearance of the disease. It may be noted also that the disease disappeared from the institutions at a time when it was highly prevalent at large in the corresponding States. Thus, judging by mortality reports, we find that in Mississippi there were 1192 deaths from pellagra in 1914, 1535 in 1915, 840 in 1916, and 1086 in 1917; that in South Carolina there were 1649 in 1915, 729 in 1916, and 714 in 1917. For Georgia no reports are available for this period, but admissions to the Georgia State Sanitarium will serve as a good index of the yearly prevalence in that State. In 1914, of 1427 patients admitted, 194, or 13.59 per cent, were active cases of pellagra; in 1915, of 1683 admissions, 272 or 16.16 per cent, were cases of pellagra; in 1916, of 1331 admissions, 111, or 8.34 per cent, were pellagra; and in 1917, of 1219 admissions, 121, or 9.93 per cent, were active cases. Clearly, therefore, the disappearance of pellagra from the institutions under consideration must have been due to something not operative at large or operative only to an inappreciable degree. Recalling the conditions of the test—namely, that hygienic and sanitary conditions (excepting diet) con-

tinued unaltered, that admission of active cases and association of these with persons in the test continued without hindrance (and was particularly frequent and free at the sanitarium), that considerable groups of persons in four separate endemic foci in three widely separated localities were involved—the something that operated to bring this disappearance about must have been the one factor, diet, close upon the modification of which disappearance of the disease followed. Since both pellagrins and exposed non-pellagrins were carried for as long as two and three years without manifesting recognizable evidence of a return or of the development of an initial attack of the disease, and since in one group of these the disease reappeared on departing from and again disappeared on returning to what, for this purpose, is considered to have been an appropriate diet, the inference seems clearly warranted that not only may pellagra be completely prevented by diet, but that it may be prevented indefinitely as long as a proper diet is maintained and without the intervention of any other factor, hygienic or sanitary. What food or foods, food factor or factors, in the diet are to be credited with the result under discussion, this experiment in itself does not definitely reveal. In planning the test diet we were guided by general observation of the character of the dietary of well-to-do people and the results of certain epidemiological observations (4) which suggested that the disease was dependent upon a diet that was faulty and that this fault was, in some way, either prevented or corrected by including in the diet larger proportions of the fresh animal protein foods. The experiment may be therefore considered as, at most, suggesting that the fresh meat and milk of the diet were concerned in bringing about the protective effect.

The Transmission of Tetanus Antitoxin through the Placenta.—TEN BROECK and BAUER (*Proc. Soc. Exp. Biol. and Med.*, 1923, 20 399) state that since the antitoxin level in the mother's and child's blood is, in the majority of cases at approximately the same level it seems probable that the placenta is permeable to this antibody. It also indicated that antitoxin has a much simpler structure than the other so-called immune bodies which fail to pass this organ.

Egg Yolk in Rickets.—HESS (*Proc. Soc. Exp. Biol. and Med.*, 1923, 20, 369) concluded that egg yolk possesses marked anti-rachitic properties for animals and for infants, far more than any natural foodstuff. It is very well tolerated and can be recommended as a supplement to the dietary of even very young infants, much as orange juice is used to protect against scurvy. The yolk has also curative value but definitely less than cod-liver oil.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

MAY, 1924

ORIGINAL ARTICLES.

EXPERIMENTAL STUDIES IN ELECTROIONIC
MEDICATION.

BY GEORGE T. PACK, M.D., FRANK P. UNDERHILL, PH.D.,
AND
JOSEPH EPSTEIN, M.D., AND I. NEWTON KUGELMASS, PH.D.,
NEW HAVEN, CONN.

(From the Department of Pharmacology and Toxicology, Yale University,
New Haven, Conn.)

Introduction. The so-called electrolytic absorption of drugs has fascinated the medical physicists for more than a century. At the present time this method is quite in vogue in England and France, but has suffered neglect in America, except in the dental profession. Most of the current literature, peculiar to this field of medication, is distinctly clinical in origin; the favorable results have almost invariably been attributed to the pharmacological behavior of the introduced drug, with little consideration of the physiological effects of the electrical current *per se*. Bearing in mind the ancient aphorism, "Nature tends to effect a spontaneous cure," we decided that a goodly portion of the accumulated data to date had not been collected under control conditions so satisfactory as to warrant such sweeping laudations upon this method of administration of drugs. Consequently, a series of laboratory experiments were performed, some of which are original; others are repetitions under the standardization of controls, thus confirming and contradicting previously published results.

The Electrochemical and Electrophysical Basis. A brief résumé of electrochemical phenomena associated with this method is

necessary in order to comprehend the changes which occur within the body subsequent to the introduction of drugs through the skin by means of the electric current.

The galvanic or continuous current is applied to the phenomena which occur throughout the length of a conductor, the two ends of which are maintained at different potentials by an electromotive force. The typical continuous current is that obtained from an ordinary galvanic cell consisting of two metals immersed in a conducting liquid. If we connect the free ends of the two metals (the so-called poles or electrodes) a continuous electric current is produced. If we insert the human body (a conducting medium) in the circuit then the current will flow in the same direction. The point of entrance of the current is the anode or positive pole and the point of exit, the cathode or negative pole (Fig. 1).

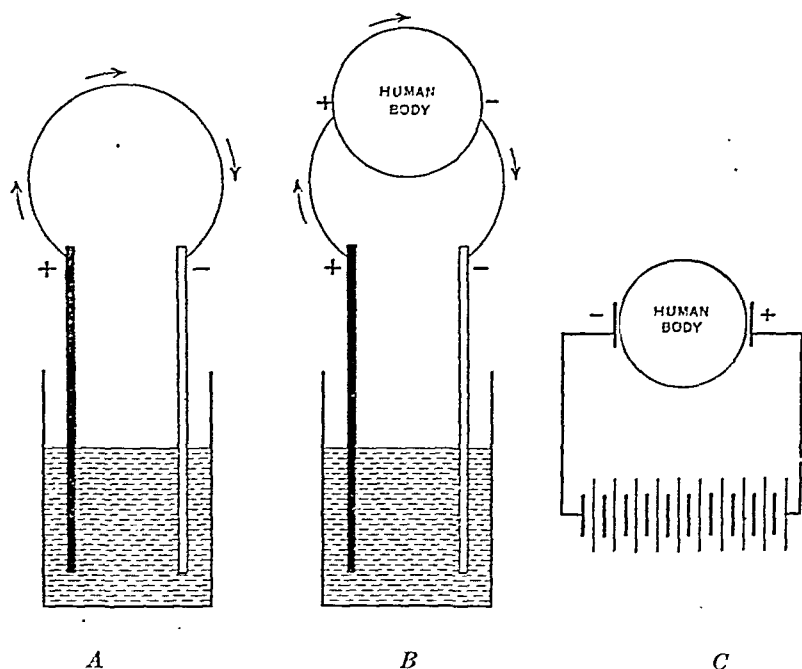


FIG. 1.—A, the galvanic cell (the arrow indicates the current course); B, the human body in the current circuit of a galvanic cell; C, the human body in a galvanic battery circuit.

Conducting media of the electric current are aqueous solutions of acids, bases and salts. Arrhenius demonstrated that these substances (electrolytes) are dissociated or split in water into their constituent atoms or groups of atoms called ions, which carry a positive charge or negative charge of electricity. Each molecule of the electrolyte furnishes two kinds of ions with equal and opposite charges of electricity.

The current remains constant so long as the potential at the extremities of the conducting medium remains constant and may be graphically portrayed (Fig. 2).

The current loses in strength because of resisting forces opposing it. The strength of the current that is actually effective in the animal body, therefore, will increase with the number of galvanic

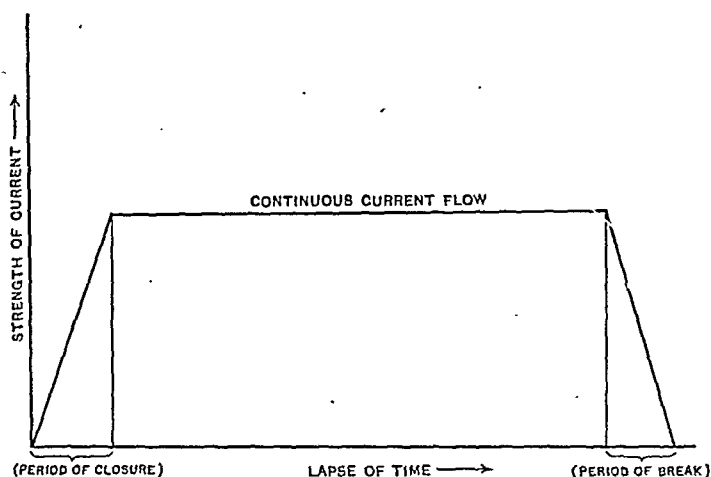


FIG. 2

cells, and will decrease with the resistance offered, and *vice versa*. Ohm's law formulates this as:

$$\text{Current strength (ampères)} = \frac{\text{Electromotive force (volts)}}{\text{Resistance (ohms)}}$$

The body resistance is variable and among the tissues the skin's resistance is greatest. The resistance of the skin is less when moistened, especially over sweat-gland ducts or hair follicles, as shown by the use of colored ions, the glandular orifices being the site of the colored deposit. The order of resistance of animal tissues is bone > fat > tendon > skin > muscle > blood > nerve.¹ The smaller the surface of the electrode in contact with the skin the more the lines of electric flux are concentrated in passing through the tissue immediately subadjacent to the electrode (Fig. 3).

Considering the body tissues as aqueous ionic solutions, the physicochemical effects of the electrical current upon solutions of electrolytes are:

1. Orientation of ions.
2. Penetration of ions.
3. Electrolysis.

1. *Orientation of Ions.* Solutions of electrolytes contain ions and molecules all in dynamic equilibrium among themselves and in constant motion. With the passage of a current through such a solution, a rearrangement of the ions results at once: The positively charged ions (cations) are repelled from the positive and attracted by the negative pole (cathode); the negatively charged ions (anions) are repelled from the negative and attracted to the positive pole (anode). "Likes repel and unlikes attract." The

effect then is simply directive, and this migration of the ions represents to us that which we call an electric current in an electrolyte.

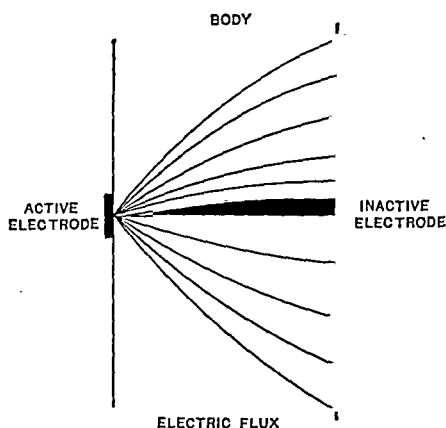


FIG. 3

2. *Penetration of Ions.* We are indebted to Hittorf for the discovery that there is a wide variation in the velocity with which the various ions migrate through the electrolyte, *e. g.*, the hydrogen ion moves about five times as fast as the chlorine ion. Knowing that the electric current is transmitted through the electrolyte wholly by the charges carried by the moving ions, Kohlrausch, by quantitatively estimating these electric charges per unit of time, was able to deduce the velocity of the ions themselves in aqueous solution. This fact has therapeutic import, as we shall see later.

THE PENETRATION OF SALTS.

<i>Anode.</i>	<i>Body.</i>	<i>Cathode.</i>
$M^+ M^+$	$Na^+ Na^+ Na^+ Na^+$	$M^+ M^+$
$R^- R^-$	$Cl^- Cl^- Cl^- Cl^-$	$R^- R^-$

BEFORE THE PASSAGE OF CURRENT.

<i>Anode.</i>	<i>Body.</i>	<i>Cathode.</i>
M^+	$M^+ Na^+ Na^+ Na^+$	$Na^+ M^+ M^+$
$R^- R^- Cl^-$	$Cl^- Cl^- Cl^- R^-$	R^-

AFTER THE PASSAGE OF CURRENT.

Although the quantity of the substances separating at the electrodes is proportional to the quantity of the current, the migrational velocity of the ions is independent of this electrical force, according to Hittorf. (Many of these ions are lost, only a portion of them migrating or transferring; the quantity of cations and anions of this latter number, however, has an equal ratio to that of the migrational velocity of cations and anions.) Hittorf, moreover, found that the concentration of the solution is the all-important factor. We are cognizant of this fact—that the greater the

degree of dissociation of the solute, the greater the facility with which the current travels, since the conductance of a solution is due to the dissociated parts of the molecules.² Hittorf further found that the large number of undissociated molecules in the concentrated solution offered a considerable degree of resistance to the motion of the ions among them. This resistance may be overcome by increasing the dilution (and consequently the degree of dissociation) until a certain point is reached where dissociation is complete and the maximal value of electrical conductance is obtained. This serves to demonstrate to us the fallacy in the use of concentrated solutions of drugs at the electrodes.

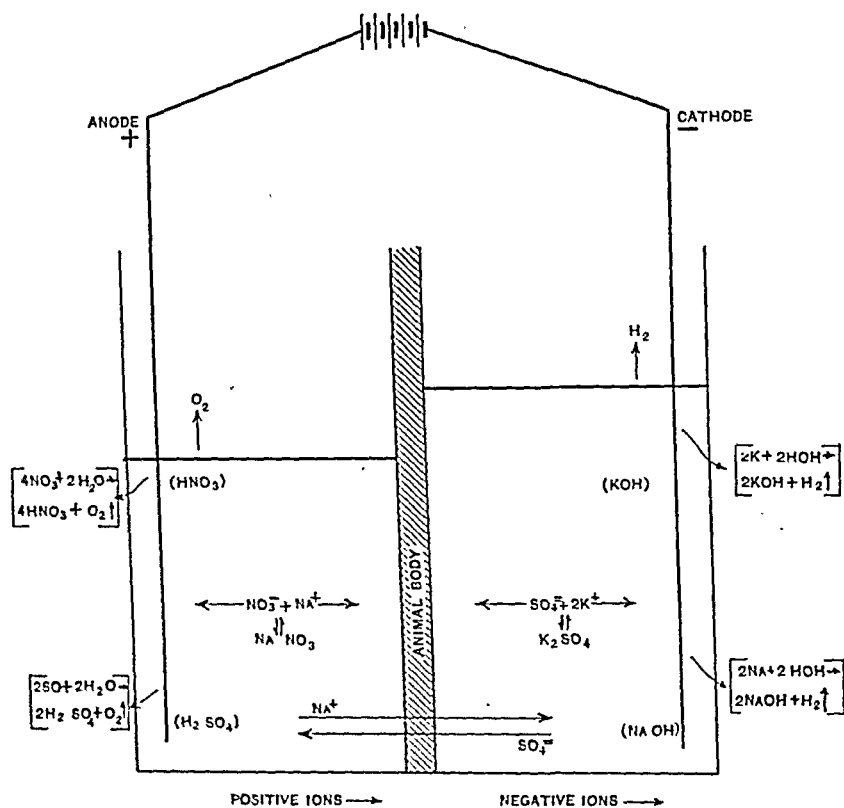
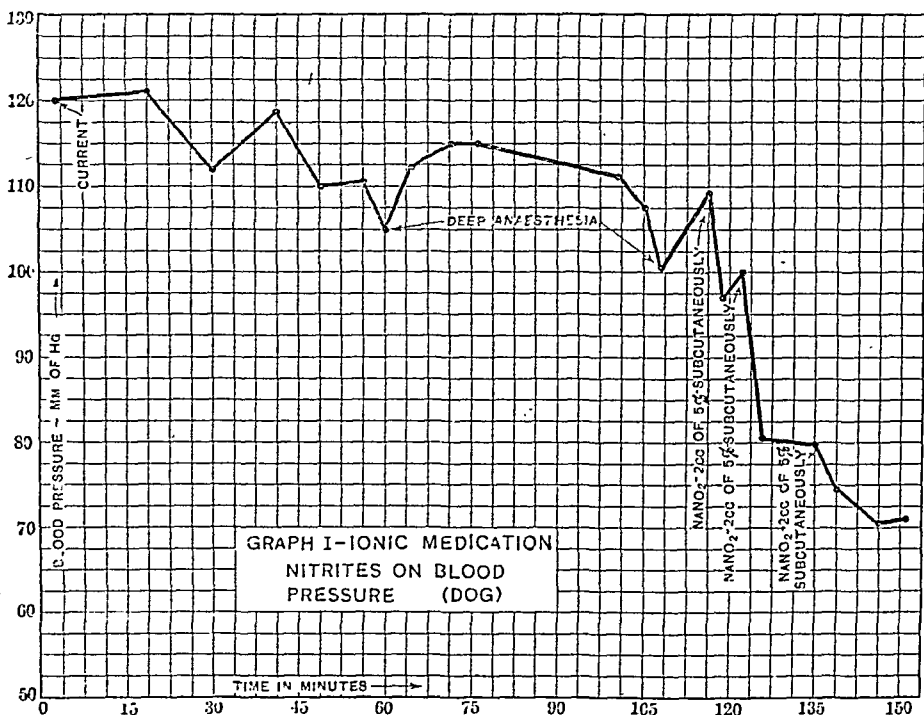


FIG. 4

We may state then that the percentage of the solution used is unimportant (provided it is dilute enough), since the quantity of ions introduced into and through the skin is more or less proportional to their chemical equivalents.³ Quite at variance with the velocity of the ions, the number of migrating ions is dependent on the quantity of current—the milliamperage—since more ions are necessary to transport the electrical charges. The migrational velocity is important, nevertheless, in the passage of the current, since the quicker moving ions convey the greater part of the current, *c. g.*, hydrogen ions carry five times the quantity of electricity that is carried by chlorine ions.

3. *Electrolysis.* Permit one arm of the body to be immersed in a solution of NaNO_3 at the positive pole, with the other arm in a K_2SO_4 solution at the negative pole. The attraction and repulsion of anions and cations by anode and cathode may then be graphically portrayed (Fig. 4). The Na and SO_4 ions are the migratory ions within the body. When these ions reach the electrodes of their respective destinations (assuming that the body is a permeable and conducting medium) they give up their charges and consequently are released in the electrically neutral state. Having lost their charges, they unite with water forming NaOH around the negative pole and H_2SO_4 at the positive pole. These changes are indirectly the secondary effects of the electric current (Fig. 4).



Since platinum is an inactive electrode, these chemical changes at the poles are devoid of particular significance, providing platinum is utilized, although in time a polarization and a consequent antagonistic polarization current may develop. However, if the electrode is a soluble one it will react chemically with the acid or base and consequently may interfere with the success of the experiment. In some instances the electrode is intentionally composed of the same metal as the cations of the medicament to be introduced, in which case the continuous solution of the electrode by newly formed acid occurs. This is desirable, since it augments the supply of these particular ions within the solution; for example, a positive zinc electrode in a solution of zinc sulphate.

To use other than an inactive electrode, except in the above instance, complicates the study of this method of introducing drugs. Metals higher in the electromotive-force series displace inferiorly placed metals from their salts; thus, a zinc electrode in a solution of mercuric nitrate deposits mercury and forms zinc nitrate, which then assumes the role of electrolyte.

Experimental Procedure. The electrodes are applied to the human body by one of two methods. The arms or legs may be immersed in separate solutions, which in turn are in contact with the electrodes. One solution contains the medicament to be introduced through the skin, the other solution being 1 per cent NaCl. The positive or negative electrode is utilized according to whether the desired ion is cation or anion.

The other method is the employment of thick layers of lint, saturated with the solution, between the skin and electrode. The introducing pole is placed over that area of skin, through which the drug desires ingress. The opposite pole may be placed anywhere on the body. We have mentioned the concentration of acid and alkali forming at anode and cathode. To circumvent the deleterious action of these caustics upon the skin, very thick layers of lint must be employed, or a porous cup may intervene between electrode and lint (Inchley).⁴ The lint must be applied smoothly, contact being even, otherwise a burn may result.⁵ An instance of this may be cited in Rolfe's careful adaptation of sheet-zinc electrodes to fit in the folds of the nates during the treatment of pruritus ani.⁶

The quantity of current comfortably tolerated by the patient is 2 or 3 ma. (Fowler⁷ used 20 to 30 ma. for one-half hour.) A greater milliamperage provokes decidedly unpleasant sensations of burning, pricking and throbbing. The larger the electrodes, the less discomfort attends the passage of the current. Some therapists advise using a current of 2 or 3 ma. per 1 sq. cm. of electrode surface.⁸ The quantitative factor in this mode of drug administration is not only the strength of current, but also the duration of its passage. The product of the number of milliamperes per 1 sq. cm. of electrode contact, by the time of the passage of the current, gives a figure which is approximately proportional to the number of ions introduced,⁸ *e. g.*, 1 ma. for thirty minutes is equivalent to 2 ma. for fifteen minutes.

What voltage is necessary for the success of this procedure? If we recall Ohm's law we may then realize that the voltage employed depends upon the resistance of the individual. The human body is remarkably resistant to the passage of the electric current. Voltages of 60 to 110 have been used by other investigators, but 20 to 30 volts have proven ample in our experiments on lower mammalia. The electrodes, of course, are in apposition with the skin before the current is turned on, the milliamperage and voltage

being gradually increased from zero to the desired amount and as slowly decreased at the completion of the treatment. This prevents shock and permits the tolerance of a stronger current.

The drug should be dissolved in the preparation to make a 1 per cent solution.

In the human experiments the immersion method only was used. With dogs as the experimental animals, the topical applications of lint upon abdomen and chest were employed.

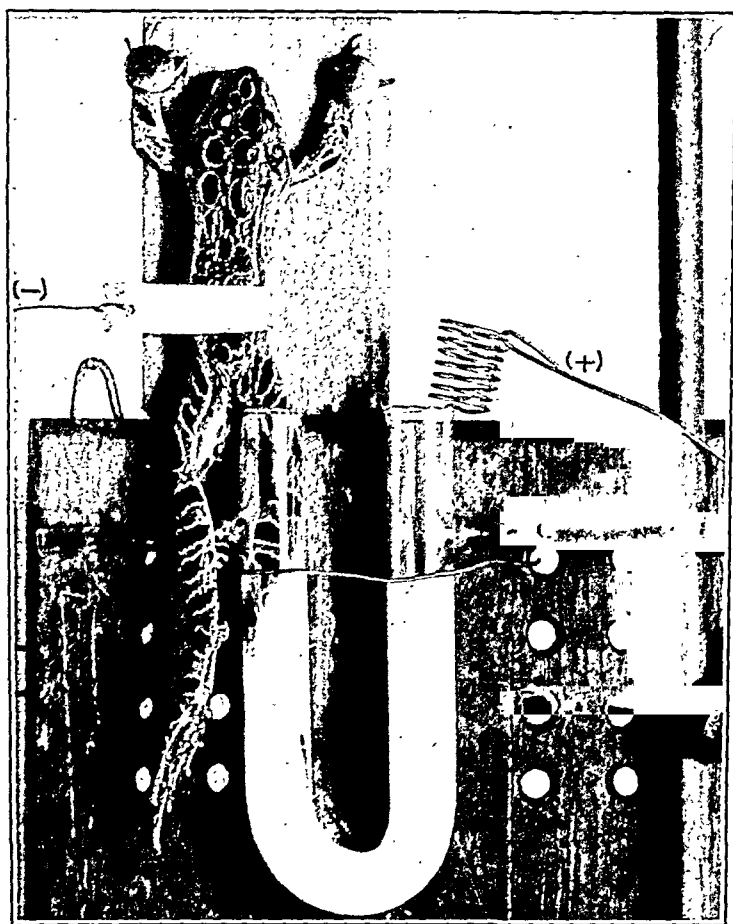


PLATE I

Plate I demonstrates how frogs were arranged. The live frog is suspended, one leg dipping into one arm of a U-tube, which contains the solution of the drug. The other arm of the U-tube holds platinum electrode. The opposite pole is a metal band upon lint surrounding the abdomen. The rheophores may be seen leading to the source of the current. Symptomatology was the only criterion of the success of this measure. We realize that the skin of the frog is not comparable to human dermis, because it is more permeable, and in addition has under it numerous lymph sacs which facilitate systemic absorption. Nevertheless, the relative rapidity

of absorption with and without the electric current is instructive and conclusive.

The mode of procedure with the rabbit: The unnarcotized animal is placed upon a rabbit board. The dependent ears are placed within two beakers. One beaker contains a solution of the drug, the other a 1 per cent solution of NaCl. Platinum electrodes immersed in the solutions connect with rheophores to the source of the current.

The methods of procedure may be tabulated as follows:*

1. The influence of the electric current upon the absorption of metals.
2. The influence of the electric current upon the absorption of alkaloids and glucosides.
3. The influence of the electric current upon the absorption of halogens, non-metals and acids.
4. Detoxication of the body by means of the electric current.
5. The treatment of experimental infections by electrolysis.

The Influence of the Electric Current upon the Absorption of Metals.

MERCURY. Because of the many disadvantages attending the administration of mercury in the treatment of syphilis, we deemed it opportune to test the efficiency of this method. Dogs and rabbits were the experimental animals. A typical protocol is submitted.

EXPERIMENT VI.—Rabbit II; weight, 1.4 kg.

Purpose. Introduction of mercury into the body by the electric current.

Conditions. Voltage, 20; milliampèrage, 7; electrodes, platinum; time, two hours daily for three days.

Methods. The rabbit ears were immersed in two beakers containing respectively NaCl (1 per cent) and $\text{Hg}(\text{NO}_3)_2$ (3.2 gm. per 100 cc) M/10. The negative pole was inserted in the former solution, and the positive pole in the latter.

Remarks. After five minutes small corroded areas began to form on the positive ear. They were seen to commence in a form resembling small red blisters about 2 mm. in diameter, with a white mucoid-like pin-point area in the center. Many of these coagulated blisters later became confluent. These lesions may be attributed to phenomena induced by the passage of the current, inasmuch as similar lesions by current and control immersions were not provocative of any disturbances.

Symptoms. Symptoms indicative of mercurial poisoning (nephritis, stomatitis, diarrhea) did not appear. Daily urine analyses over the period of a week did not detect mercury by such methods

* In every case the experiment was carefully controlled by noting: (a) The influence of the electrical current *per se*, and (b) the effect of similar applications of the drug without the aid of the electrical current. Any experiment cited is merely an illustrative example of a series of confirming experiments.

as the Reinsch, potassium-iodide and zinc-amalgamation tests. Feces were likewise negative.

Similar negative results were found in 2 dogs and 5 other rabbits. The explanation is, no doubt, the same as Turrell's excellent reasoning for the non-absorption of zinc:⁹ "The zinc ion attracted from the positive electrode to the negative pole, on arriving at the surface of the body, lags behind, and the current is carried on much faster by the H ions of the tissues. The zinc ion is thus free to enter into chemical combination with the tissue constituents and forms an oxychloride of zinc, which is electrically deposited upon the superficial tissues. The process is one of electrodeposition, resembling electroplating of commerce. . . . The skin or mucous membrane thus forms a 'virtual' negative pole." This is exactly what happens in the experiments with mercury. As long as the mercuric ions are electrically charged they do not chemically unite, but as soon as they lose their charge they form mercuric-proteinate with the tissues. This coagulation occurs quite superficially, but in time is redissolved in the body fluids. Turrell¹⁰ quotes Sir Oliver Lodge as saying: "The procession of ions continues until it meets with some discontinuity—either some change of liquid or some solid conductor. At a change of liquid, another set of atoms continues the convection." He further cites Chatsky's experiment, as confirming the theory that when a change of liquid occurs in the interpolar path there is a transferal of electrical charges by the ions. It is our belief that this obstacle occurs quite frequently, due to such things as the superficial circulation in the skin, lymph currents, etc.

Cross,⁵ by an experiment *in vitro*, concludes that the slow migration of the lead ion is due to its precipitation with salts of the tissue. He simulates the colloidal-tissue fluids by using a solution of gelatin in tap-water. We must agree that the body is a complex electrolyte.

We believe also that the relief experienced in the stiff joints of rheumatoid arthritis by the ionization treatment with the mercuric ion of mercuric succinimide (Clark) is due to the electric current itself, and not to the introduction of the mercuric ions.

ZINC. Although we did not use zinc in our experimentations, yet it is considered here because it proves that the heavy metals are efficient only for local therapy and not for systemic administration, *i. e.*, by the electroionic method. Dilute solutions of ZnCl_2 or ZnSO_4 applied at the positive pole have been reported by Friel¹¹ as beneficial or curative in the following conditions: Empyema of maxillary, frontal and sphenoidal sinuses, impetigo of face, eczema, ulcers of arms and legs, chronic otorrhea.¹² Rolfe⁶ uses zinc ionization in the treatment of pruritus ani, while Clark⁸ enumerates a host of localized lesions for which zinc therapy has been employed.

TREATMENT OF TUMORS. Borrel *et al*¹³ treated implanted sarcoma in rats by fixing positive carbon electrodes on compresses saturated with various metallic solutions over the tumor. Curative results were obtained in a number of instances, especially by the lead ion. Disappearance of a cancer of the rectum has been reported, by Wardle,¹⁴ subsequent to zinc ionization, using a current of 60 ma. for thirty minutes on alternate days. Clark removes multiple warts by magnesium ionization. It is agreed that the metals deposited on the surface of the tumor are somewhat corrosive, but the destructive action is probably not due to this alone. Referring to the above protocol, it is noted that even a millampère-*age* of 7 produces coagulative phenomena. A millampère-*age* of 60 would be quickly destructive. Liquefaction occurs at the negative pole; coagulation at the positive. This latter phenomenon is utilized in the coagulation of blood in aneurysmal sacs by electrolysis. All of these facts lead us to believe that the good results obtained in the treatment of tumors, and the various local lesions mentioned, are due in large part to the action of the electric current *per se*.

MAGNESIUM (CALCIUM ANTAGONISM). Magnesium anesthesia cannot be induced in the rabbit by ionic medication. Success was obtained with frogs as the experimental animals. Control immersions were unproductive of any symptoms.

EXPERIMENT XXV.—Frogs.

Purpose. (a) To induce anesthesia by the introduction of magnesium into the body by the electric current; (b) to antagonize magnesium action by calcium similarly exhibited.

Conditions. Voltage, 10; millampère-*age*, 0.5; electrodes, platinum. Time: Part *a*, six minutes; Part *b*, seven minutes.

Methods. The frog was placed within the circuit, after the arrangement illustrated in Plate I. MgSO_4 (5 per cent) was placed within the U-tube at the positive pole. Later CaCl_2 (5 per cent) replaced the magnesium sulphate solution.

Symptoms. One and a half minutes after the initiation of the current flow, the respiration became quite rapid, subsiding quickly to extremely slow ones. Flaccidity was noted at the two-minute interval. At six and a half minutes the frog was entirely flaccid. The animal was narcotized and anesthetized, as judged from the response to stimulation. Pupils were contracted to the degree of narcosis. At this point the MgSO_4 was removed and the CaCl_2 substituted. One-half minute later the pupils began to increase in size. The animal again responded to stimulation. Recovery had evidently occurred. However, seven minutes subsequent to the calcium substitution, the frog became quite stiff. The pupils were again contracted. Examination revealed that this condition was not a true spasticity, but a rigor, which probably accounts for the terminal pupillary and skeletal muscle changes.

Remarks. The systemic symptoms are attributed to lymphatic absorption, subsequent to the introduction of these metals through the skin. The Mg-Ca antagonism was earlier discovered by Meltzer.

BARIUM. Experiments with barium chloride were negative, although conducted in a manner identical with the above. The end-point desired was the death of the animals with the ventricles in systole and the auricles in diastole.

The Influence of the Electric Current upon the Absorption of Alkaloids — Neutral Principles, Etc. **STRYCHNIN.** Stephen Leduc, the father of electroionic therapy, first produced strychnin convulsions in a rabbit by "driving" in the strychnin ion by means of the galvanic current. Inchley⁴ has recently confirmed this, but has modified Leduc's theory by stating that strychnin is fatal because it is carried by the blood stream from the superficial tissues to the spinal cord. A protocol of one of our typical experiments is as follows:

EXPERIMENT XXI.—Rabbit; weight, 1.8 kg.

Purpose. To introduce strychnin into the body by the electric current.

Conditions. Voltage, 20; milliampèrage, 12.5; time, 6.38 to 7.40 P.M. (sixty-two minutes).

Procedure. Ears of rabbit were immersed in beakers; positive pole, beaker of 2 per cent strychnin sulphate; negative pole, beaker of 1 per cent sodium chloride.

Observations. 7.00: Definite general hypersensitiveness to touch; reflexes very acute; twitches to stimulation; marked defecation.

7.40: Sudden opisthotonic convulsion with cessation of respiration.

7.45: Rabbit removed from board; body is stiff and arched; this gradually was replaced by tremors and finally flaccidity; another convulsion followed, during which death occurred at 8.00 P.M.

Remarks. Control experiments of (a) immersion and (b) current alone were negative.

EXPERIMENT XXIV.—Frog.

Purpose. Strychnin introduction, as above.

Conditions. Voltage, 20; milliampèrage, $\frac{1}{2}$.

Procedure. (Plate I.) Two per cent strychnin sulphate at positive pole in U-tube.

Observations. 10.38 to 10.40: Current on.

10.40: Current off; leg washed thoroughly.

10.50: Hypersensitiveness.

11.00: Typical convulsions.

Control. No current used; leg immersed as above.

10.59 to 11.01: Leg immersed in 2 per cent strychnin sulphate.

- 11.01: Leg washed thoroughly.
 11.35: Slight hypersensitiveness.
 11.55: More hypersensitive.
 12.45: Typical convulsions.

Remarks. The difference in the rapidity of the onset of convulsions may be attributed to the influence of the electric current.

PICROTOXIN. EXPERIMENT XXXII.—Frogs.

Purpose. Picrotoxin introduction through the skin by the electric current.

Conditions. Voltage, 20; milliamperage, $\frac{1}{2}$.

Procedure. (Plate I.) Two-fifths per cent picrotoxin at positive pole in U-tube.

Observations. 4.29 to 4.35: Current on.

4.32: Hypersensitive.

4.35: Current off; typical convulsions; picrotoxin croak, etc.

Control. 4.40 to 5.10: Leg immersed in 0.4 per cent picrotoxin; no current.

5.10: Convulsions.

Remarks. The electric current hastens the skin absorption of picrotoxin; picrotoxin is a poor electrolyte.

VERATRIN. EXPERIMENT XII.—Frogs.

Purpose. Veratrin introduction through the skin by electric current.

Conditions. Voltage, 20; milliamperage, $\frac{1}{2}$.

Procedure. (Plate I.) Two per cent veratrin at positive pole in U-tube.

Observations. 5.29 $\frac{3}{4}$ to 5.30: Duration of current and immersion of leg.

5.31: Characteristic veratrinization. Frog is clumsy. Muscles contract well, but do not relax.

Control. 10.35 to 10.36. Leg immersed in 2 per cent veratrin solution.

10.45: Definite signs of veratrin action on skeletal leg muscle.

Remarks. Veratrin is absorbed very quickly by the frog skin, but much more quickly with the aid of the galvanic current.

NICOTIN. Nicotin is absorbable by human skin. It is quite rapidly absorbed from mucous membranes, hence is likewise absorbed with ease by the frog's skin.

EXPERIMENT XXII.—Frogs.

Purpose. The absorption of nicotin through the frog's skin with the aid of the electric current.

Conditions. Voltage, 20; milliamperage, $\frac{1}{2}$.

Procedure. (Plate I.) One-twenty-fifth per cent nicotin placed at positive pole in U-tube.

Observations. 11.12 to 11.15: Current on and leg immersed.

11.15: Current off; leg rinsed.

11.25: Nicotin convulsions; clonic; independent of sensory stimulation.

Control. 11.28 to 11.31: Leg immersed; no current.

11.31: Leg rinsed.

12.20: Individual muscles are hypersensitive; fine tremors like fibrillations; no convulsions.

Remarks. The electric current facilitates the absorption of nicotin.

CURARE. Rabbits could not be curarized by means of the galvanic current, although a milliampèrage of 12 for one and a half hours was used.

EXPERIMENT XXIII.—Frogs.

Purpose. To introduce curare through the skin by means of the galvanic current. Identification by a duplication of Claude Bernard's classical experiment.

Conditions. Voltage, 20; milliampèrage, $\frac{1}{2}$.

Procedure. (Plate I.) Both sciatic nerves were exposed as high on thigh as possible. One leg was ligated tightly, leaving the nerve excluded from the ligature. The unligated leg was immersed in 0.5 per cent curare at the positive pole.

Observation. 10.00: Immersion and current on.

10.05: Diminished response of unligated leg to sciatic stimulation.

10.07: Definite curarization.

Symptoms. (a) Stimulation of sciatic nerve of ligated leg; contraction of gastrocnemius of ligated leg; the ligation prevents the curare from reaching the myoneural junctions *via* the circulation.

(b) Stimulation of sciatic nerve of unligated leg; corresponding gastrocnemius does not contract, but muscle of ligated leg weakly responds; this is a reflex through the spinal cord, since the sciatic nerve contains both motor and sensory fibers.

Control. Prepared exactly as above. Leg immersed for nineteen minutes; no action.

PILOCARPIN. EXPERIMENT XXIX.—Rabbit; weight, 1.7 kg.

Purpose. To introduce pilocarpin into the body by means of the galvanic current.

Conditions. Voltage, 20; milliampères, 13; time, 2.55 to 3.40.

Procedure. Rabbit's ears immersed; positive beaker, 0.4 per cent pilocarpin hydrochloride; negative beaker, 1 per cent sodium chloride.

Observations. 2.55: Immersion; current on.

3.20: Definite salivation and epiphora.

3.40: Sialogogue action marked (saliva drips from mouth); epiphora increased; the pupils were not contracted; heart-rate is normal; these latter two findings engender doubt as to whether pilocarpin is actually introduced; however, the accelerated glandular activity is suspicious.

Control. Negative for immersion of ears in pilocarpin solution.

CAFFEIN. EXPERIMENT XXXVI.—Rabbit; weight, 2.1 kg.

Purpose. To produce diuresis by the electrolytic introduction of caffein through the skin.

Conditions. Voltage, 20; milliampèrage, $12\frac{1}{2}$; time, two hours.

Procedure. Controls were first run on the same rabbit; each rabbit was deprived of food and water for ten hours previous to the experiment; the normal two-hourly output averaged from 1 to 3 cc of urine; ears were immersed; positive beaker contained 1 per cent caffein citrate; negative beaker contained 1 per cent sodium chloride; upon removal from the rabbit board, the animal was catheterized every two hours and the volume carefully measured.

Results. Control rabbits and those utilized in the experiment alike secreted an average of 1 to 3 cc of urine every two hours; not enough caffein was introduced to modify the secretory activity of the kidney.

LOCAL ANESTHETICS. These confirm the restriction of value of ionic therapy to local areas.

(a) COCAIN. Human subject.

Purpose. To produce local anesthesia by the introduction of cocain into the skin.

Conditions. Voltage, 20; milliampèrage, 2.

Procedure. Immersion method. One finger in beaker containing 1 per cent cocain hydrochloride at positive electrode; another finger in negative beaker containing 1 per cent NaCl.

Observation. 3.17 to 3.27: Current period.

3.27: Finger definitely anesthetized and numb; feels asleep; pain not completely absent over entire area of immersion.

4.30: Skin still numb.

4.50: Skin has regained normal sensitivity.

Controls. (a) Immersion in 1 per cent cocain solution without the current gives negative results.

(b) The current by itself produces a prickling sensation.

Remarks. This method has been used clinically. The directions call for 3 ma. of current per 1 sq. cm. of surface immersed. Fette³ states that cocain anesthesia by the electrolytic method lasts four to five hours; the reason for the relative prolongation of local anesthesia by this method over that of hypodermic injection, he attributes to the following facts: Cocain, given hypodermatically, is carried away very quickly by the lymph; in the electrolytic method of absorption all osmotic conditions are dominated, and

the cocain enters the cells instead of bathing them so that "the ions accumulate and remain in static equilibrium as a store supply for gradual elaboration by the protoplasm." We do not find cocain anesthesia prolonged by this method.

(b) PROCAIN. Human subject.

Purpose. To produce procain anesthesia by driving in procain into the skin by the galvanic current.

Conditions. Voltage, 20; milliampère, 2.

Procedure. Immersion method. One finger in beaker containing 5 per cent procain at positive electrode; another finger in negative beaker containing 1 per cent NaCl.

Observations. 3.38 to 3.48: Current period.

3.50: Definite numbness, but not complete anesthesia for pain.

4.30: Sensations have returned to normal.

(c) BUTYN. Human subject.

Purpose. To produce local anesthesia by the electrolytic introduction of butyn into the skin.

Conditions. Voltage, 20; milliampère, 2.

Procedure. Same as above, only positive beaker contains 1 per cent butyn.

Observations. 4.01 to 4.11: Current period.

4.12: Finger numb; same degree as with procain.

4.30: All numbness gone.

Remarks. Anesthesia is much shorter than with procain, and very much briefer than with cocain.

(d) BENZYL CARBINOL. Human subject.

Purpose. To produce local anesthesia by benzylcarbinol, electrically introduced.

Conditions. Voltage, 20; milliampère, 2.

Procedure. Same as above, only positive beaker contains 1.5 per cent benzylcarbinol.

Observations. 4.46 to 4.53: Current period.

4.53: Slight, insignificant, temporary numbness.

(e) SALICAIN. Human subject. One per cent solution. This is an extremely poor electrolyte. No action could be noted.

QUININ. The local effects of quinin, introduced into the skin by the electric current, have been reported beneficial in cases of herpes zoster. According to Jacoby,¹⁵ quinin has subsequently been recovered from the urine.

ATROPIN. Although the rabbit is markedly tolerant to atropin, Inchley⁴ causes a paralysis of the cardiac vagal endings by the introduction of the atropin ion, with the current localized in the tongue.

ACONITIN. Inchley produced delirium cordis and death in a rabbit, with the introduction of the aconitin ion, by a milliampère of 25. B. W. Richardson, in 1859, locally anesthetized skin areas with aconite by utilizing this method.

The Influence of the Electric Current upon the Absorption of Halogens, Non-metals, Acids, Etc. The halogens, non-metals and acid radicals are negative ions or anions and consequently are introduced at the cathodal pole.

CYANIDES. Leduc originally performed this experiment which has been validated recently by Inchley.⁴ These phenomena are adumbrated in the following protocol:

EXPERIMENT XIX.—Rabbit; weight, 1.6 kg.

Purpose. To introduce cyanides into the body by the electric current.

Conditions. Voltage, 20; milliamperage, 12.5.

Procedure. The ears of rabbit were immersed in beakers. Positive pole, beaker of 1 per cent sodium chloride; negative pole, beaker of 5 per cent sodium cyanide.

Observations. 5.50 to 6.25: Immersion and current on.

6.10: Tonic convulsions commence and definite air-hunger appears; the symptoms progress gradually.

6.15: Respiration is quite labored; eyeballs protrude, etc.; respiration became weaker and weaker, until the rate was only 19 per minute; the mouth was open wide and the breath came in gasps; conjunctival reflexes were absent; the animal was almost dead.

6.25: Animal removed from apparatus. Sodium thiosulphate injected subcutaneously. Venesection reveals blood of a cherry-red color.

Remarks. The cyanide ion easily enters at the negative pole. Systemic absorption *via* circulation completes the introduction. Attention is called to the fact that by this method the cyanide ion is only gradually absorbed, so that the sequence of symptoms are well portrayed.

Control. Ears immersed for one hour in solutions of identical character and strength; the electric current was not used; no symptoms developed.

NITRITES. The subcutaneous administration of 1 grain of sodium nitrite is sufficient to produce a fall in blood-pressure of 10 to 12 mm. of mercury. That the characteristic vasodilation does not follow the electrolytic method of absorption, is apparent in Graph I. The nitrite ions may form a quite stable chemical union with the superficial tissues, and, in addition, the quantity or concentration of these nitrite ions absorbed by the circulation may be insufficient at any one time to provoke a noticeable pharmacological effect.

EXPERIMENT LX.—Dog; weight, 7.6 kg.

Purpose. To produce vasodilation and a consequent fall in blood-pressure by the electrolytic absorption of the nitrite ions.

Conditions. Voltage, 20; milliampèreage, 15; time, 4.05 to 5.55.

Procedure. The topical application method was utilized. Sodium nitrite (5 per cent) solution saturated the lint pad at the negative pole, which was a platinum plate 3 by 4 inches; at the positive pole was sodium chloride (1 per cent) solution. Mercury manometric readings of the carotid blood-pressure were taken. The depth of ether anesthesia was carefully regulated.

Observations. (See Graph I on page 630.)

Control. The dog was susceptible to nitrite influence as revealed by the terminal hypodermic injection.

SALICYLATES. Clark⁸ tabulates the pathological conditions, for the treatment of which a 1 per cent solution of sodium salicylate is used at the negative pole: Myositis, lumbago, sciatica, trigeminal neuralgia, chronic rheumatism and gout. Each rheumatic joint is treated locally, so that, theoretically, beneficial results are not dependent on the presence of the salicyl ion in the general tissues. Inchley,⁴ employing a current of 25 milliampères, through an electrode of 20 sq. cm., was not able to introduce the salicyl ion deeper into the joint than occurred with the hypodermic administration of sodium salicylate. The depth of penetration was ascertained by staining the excised tissue with ferric chloride. Insomuch as the deeper-joint structures were unstained, we might infer that this is fallacious therapy. Cross⁵ attributes the benefits from salicylate ionization as due to "drastic tissue disturbances, rather than the chemical effects of the specific ion, *e. g.*, in sciatica 15 ma. are necessary to insure relief."

Inchley was able to recover 0.8 mg. of salicylate in the urine at the completion of the first thirty minutes of the above quoted experiment. Evidently a certain amount of circulatory absorption occurs. We, like Maute, were unable to confirm these urinary findings.

The following experiment was planned with the purpose of demonstrating whether sufficient salicyl ions can be introduced to produce systemic effects.

EXPERIMENT XXXVIII.—Rabbit; weight, 2 kg.

Purpose. To test the antipyretic power of the salicyl ion, introduced by electrolytic absorption from the skin.

Conditions. Voltage, 20; milliampèreage, 12.5; time, 11.00 A.M. to 1.00 P.M.

Procedure. Albumose fever was attempted by hypodermic injections of Witte peptone. This was not so productive of pyrexia as were bacterial emulsions of *Bacillus coli*, given intraperitoneally. The temperatures in our series of 3 rabbits rose to approximately 41° C. (rectal) from a normal temperature of about 38.5°. The rabbit was placed on animal board. Ears immersed. Positive beaker contained 1 per cent sodium chloride; negative beaker contained 1 per cent sodium salicylate.

Controls. The drop in temperature at first was considered specific. However, the same occurred by using sodium chloride solution at both poles. A control, with the rabbit in position on the board only, and no electric current, causes us to believe that the fall in temperature is due to the vascular changes induced by the rabbits' position on the board.

Analysis. Urinalysis is negative for salicylates.

IODIDES. Theodore Clemens, in 1858, was the first physician to advocate the clinical use of the electrolytic transmission of iodine. His purpose was to further the lysis of syphilitic scleroses. A few of the pathological conditions for which the electroionic application of iodine has been reported efficacious are: Localized syphilitic infections, lead palsy, labyrinthian deafness, small skin and mucous membrane tumors,¹⁵ certain iodine-deficient goiters,⁸ cicatrices, keloids¹⁶ and pruritus ani.⁶

Iodine has been detected in the urine subsequent to its electrolytic introduction. Bourguignon, by experiments upon himself, quantitated the daily urinary excretion of iodine. By employing 10-ma. current for three minutes daily he was able to recover 6.4 mg. of iodine in the twenty-four hour urine sample. However, as Turrell says, the presence of iodine in the urine does not confirm its deep penetration in the local area of application.

EXPERIMENT XI.—Human.

Purpose. To introduce I from NaI into a human subject.

Conditions. Voltage, 20; milliamperage, 2; time, fifteen minutes.

Procedure. Five per cent NaI on negative pole; hand and wrist immersed. One per cent NaCl on positive pole; hand and wrist immersed.

Observations. The burning and tingling sensation at the positive pole is decidedly unpleasant.

Results. Urinalysis on three subsequent days were negative for iodine.

Remarks. This is contradictory to Bourguignon's findings. The number of milliamperè minutes ($10 \text{ ma.} \times 3 \text{ min.} = 30$ and $2 \text{ ma.} \times 15 \text{ min.} = 30$) are the same, hence theoretically a proportionate amount of iodine should be absorbed. The negative findings here can probably be attributed to the short duration of the experiment.

That iodine is electrolytically absorbed from the skin is an actuality. Witness the following protocol:

EXPERIMENT XV.—Rabbit; weight, 1.3 kg.

Purpose. To introduce I from KI through the skin by means of the galvanic current.

Conditions. Voltage, 20; milliamperage, $7\frac{1}{2}$; time, 2.45 to 4.45 P.M.

Procedure. Rabbit ears immersed. Potassium iodide (4 per cent, in negative beaker; sodium chloride (1 per cent) in positive beaker.

Results. 5.00 P.M.: Rabbit catheterized; urine gave strongly positive iodine test.

April 4, 1923. 10.00 A.M.: Urine positive for iodine.

April 5, 1923. 10.00 A.M.: Urine positive for iodine.

Controls. These were negative. Immersion of rabbit ears in a concentrated solution of iodine (5 per cent) in KI solution (4 per cent) for two hours, was not attended by sufficient absorption of iodine, to be detected by excretion in the urine.

Remarks. Iodine is readily absorbed through the skin from an ointment or alcoholic medium, but not from an aqueous solution. The galvanic current greatly facilitates the ingress of the iodine ion from the latter solution.

Detoxication of the Body by Means of the Electric Current. W. I. Morton suggested that, inasmuch as ions can be driven in through the skin, a reversal of current might be an efficient means of detoxicating the body from such poisonous metals as lead and arsenic. This theoretical suggestion has found clinical expression in the so-called electrolytic treatment of lead poisoning, wherein the patient is partially immersed in a weak saline solution at the negative pole. We have been unable to find data confirming the exodus of lead.

Actuated by the above, we experimentally poisoned rabbits with mercuric acetate and attempted to withdraw some of the mercury ions through the skin of the ear of the rabbit. At frequent intervals the beaker at the negative pole was tested for mercury. In no instance was mercury found.

The hypothesis is without merit. The relative proportion of mercury or lead ions with the other ions normally present in the tissues is infinitely small. Must we suppose that the electrical charges have a specific affinity for the mercury or lead ions? This is manifestly untrue for two reasons. There are many ions (such as H ion) within the tissues that migrate with a much greater velocity than does lead or mercury, hence these would carry the majority of the electric charges. Again mercury and lead form somewhat insoluble organic salts (albuminates, etc) which do not ionize, and in addition remain intact within the body for a long period of time.

EXPERIMENT XVI.—Rabbit; weight, 1.5 kg.

Purpose. To detoxicate the body of the iodine from sodium iodide.

Conditions. Voltage, 20; milliampèreage, 10.

Procedure. Rabbit's ears were immersed in two separate beakers. Both beakers contained sodium chloride solution (1 per cent).

Positive electrode in one beaker and negative electrode in the other.

10.28: Five grams of sodium iodide in solution were given by stomach-tube. Samples of fluid were taken at intervals from the beaker at the positive pole and tested for iodine.

Observations. 10.55: No iodine demonstrable.

12.00: Very faint iodine test.

12.15: Definite positive starch test for iodine.

Remarks. This experiment was verified several times. The results are not as paradoxical as they may seem. The iodine ion migrates with a velocity equal to that of the chlorine ion. Furthermore the iodides exist in the circulating fluids as such and hence are available for ionic migration. The proportion of iodine to chlorine ion leaving the body to appear at the positive pole is, no doubt, the same as their relative ratio in the blood stream; so there is no selection of the iodine ions to carry the electrical charges, with the exclusion of all other ions. The human excretes some iodine in sweat; but because rabbits lack sudoriferous glands this withdrawal of iodine through the skin is all the more conclusive.

The Treatment of Experimental Infections by Electrolysis.—Pharmacologically, the iodides and nascent iodine behave differently. The latter is an efficient antiseptic, but does not exist in this form within the body. The positive pole electrolyzes the iodides releasing the resultant nascent iodine. This fact has been utilized clinically by Strandberg, later by Harris.¹⁷

Harris treated an extensive lupus ulceration as follows: The patient was given 3 gm. of NaI per os. After permitting sufficient time for the iodides to be well distributed throughout the tissues (seventy-five minutes), the positive pole (needle) was introduced into the lesion. A series of three-minute treatments, using a current of 2 ma., was required. The question here is whether or not sufficient nascent iodine is released to be of benefit.

EXPERIMENT X.—Cat; weight, 2.4 kg.

Purpose. The demonstration of free nascent iodine in muscles, by the insertion of the positive pole in the muscle, after sodium iodide has been taken by mouth.

Conditions. Voltage, 20; milliampèreage, 2.

Procedure. 4.00 P.M.: Paraldehyde (2.5 cc) and 5 gm. of potassium iodide in solution—given by stomach-tube.

4.15 P.M.: Muscle of thigh exposed and dilute starch solution injected intramuscularly. This was to permit sufficient time to elapse for the diffusion of tissue fluids and starch solution within the muscle.

4.30 P.M.: Negative electrode attached to opposite leg. Current turned on. Using platinum-wire electrode as the positive pole,

and introducing this terminal into the previously starched muscle, a definite blue coloration of the fluids occurred. This did not occur with other muscles. The color was distinctly blue and entirely different from the brown, charred areas of cautery that occasionally occur. This finding was corroborated in rabbits and white rats.

EXPERIMENTS XIII, XXVI and XXVII.—White rats and rabbits.

Purpose. To produce localized infections in rats and rabbits, and to treat these with sodium iodide per os and electrolysis within the lesions.

Procedure. Suspensions of attenuated *Staphylococcus pyogenes aureus* cultures of low virulence were employed as the infecting organisms. Series of albino rats and rabbits were inoculated with the saline suspensions of these organisms; 0.05 cc and 0.1 cc of these suspensions were injected subcutaneously into rat and rabbit ears respectively by means of a tuberculin syringe. Definite tiny wheals appeared. As a rule, variable sized localized infections appeared at the site of inoculation. These differed considerably in severity of appearance. Well-marked lesions were present in the rat's ears within twenty-four to thirty-six hours; in the rabbit's, within forty-eight hours. Some of these untreated animals served as controls. Others were treated with the electric current alone, *i. e.*, with the positive pole needle in the infected lesion. In the remainder sodium iodide was given by mouth (rabbits) and hypodermatically (rats) and the current employed for electrolysis within the lesion. In some instances only one ear was used, the other serving as a control.

Results. These may be summarized. Those treated by the release of nascent iodine at the positive pole, implanted in the lesion, fared no better than the ears subjected to the influence of the electric current alone. Any beneficial effects, as compared with the controls, may be attributed to the phenomena occurring at the positive pole, other than the release of nascent iodine. These bactericidal phenomena are: The formation of heat, the release of nascent oxygen, the production of concentrated acid and the bacteriotropical influence of the positive pole for the negatively charged protoplasm of the staphylococci. Our results tend to validate the rationality of Fowler's⁷ employment of the electrolytic bath in the treatment of septic wounds. He immerses the wound in a warm solution of NaCl and places the positive electrode in the bath. The stimulation of tissue regeneration and epithelial proliferation by the galvanic current is another modifying factor.

Discussion. Of what particular advantages can this method boast over other forms of administration? Clark⁸ and other electrotherapeutists submit the following reasons. The drugs are not subject to the digestive changes which may accompany

oral administration. With hypodermic administration, the drug follows the course of the circulatory fluids and is quickly absorbed, whereas in the electrolytic absorption method the current dominates all osmotic conditions, and the cellular membranes are penetrated by the drug. Theoretically, then, in the latter instance the cells become more saturated with the medicament. This presents strong argument for the utilization of this method of therapy in local conditions, especially since it is not always advisable to distribute the drug throughout the body, when only a local area is in need of it. Moreover, larger quantities of the medicament can be applied to the local area under treatment. It is believed by some to be attended by a more prolonged local action, although we did not find this true with the local anesthetics. The disadvantages are the pain, inconvenience, danger of burns, variability in dosage, etc.

Several decades ago this phenomenon was entirely attributed to cataphoresis. This term implies an electrical osmosis, a liquid flow from anode to cathode. This is molecular rather than ionic. It is quite a slow process. Clinicians have attempted to absorb exudates and fluid accumulations by this fluid current. It may facilitate the migration of the cation but not the anion, because the fluid flow is from anode to cathode. The specific migrational velocity of the cation may be superimposed upon the speed of the cataphoretic current, giving a picture similar to that of a man walking forward on a moving train. Cataphoresis is at present largely disregarded.

The experiments cited here are in agreement, as a rule, with the work of Turrell in England and Clark in America. Both are agreed that "ionic medication" is indicated in local conditions. Although deep ionic medication is impossible (excluding circulatory transmission), beneficial results do accrue from the ionizing action of the current alone. Clark's⁸ conclusions cannot be better stated: "The application of the galvanic current alone, without the use of remedial drugs, is often of benefit in various pathological conditions due to interpolar ionization of the tissue constituents, thereby altering nutrition, improving metabolism and producing stimulation or sedation, contraction or dilatation, depending upon the polarity of the current."

Conclusions. I. The electric current may be used as a means of driving ions into the skin. There are, however, various factors involved in this transfer, *e. g.*, the ampèreage used; the time of application; the resistance of the tissues; the migrational velocity of the entering ion, and also its chemical nature.

In the case of the heavy metals, as Hg^{++} , Mg^{++} , Zn^{++} , Pb^{++} , their ions as soon as they enter the skin give up their electrical charge to other much faster traveling ions present in the tissues, *e. g.* H , Na . The metals, then, losing their charges, enter into

combination with the protein and salts of the tissues and may form precipitates. These are redissolved too slowly to be demonstrable by the common chemical tests in the excretions. Heavy metals, therefore, may be efficient for purely local administration, but not for systemic effect.

II. The electric current facilitates the introduction of many alkaloids through the skin.

(a) Systemic effects of strychnin and pilocarpin were demonstrated upon rabbits after electrolytic administration of the drugs for approximately one hour each. Controls without the current were negative.

(b) The action of caffein and curare (as gauged by systemic effects) failed to be demonstrated upon rabbits after electrolytic administration of the respective drugs for approximately two hours each.

(c) The action of curare, picrotoxin, strychnin, veratrin and nicotin was shown to be definitely accelerated when electrolytically introduced into frogs' skin, as compared with controls.

(d) Electrolytic experiments with local anesthetics in which a current of 2 ma. was used for ten minutes upon a human subject showed that:

1. Cocain produced moderate but incomplete anesthesia of finger lasting about one hour.
2. Procaïn and butyn produced mild anesthesia lasting about one-half hour.
3. Benzylcarbinol and salicain failed to produce any significant anesthesia.

III. Halogens, non-metals and acids, being anions are introduced by anaphoresis. The ingress of some is demonstrably accelerated by the electric current (CN, I_2), while in others there could not be demonstrated any acceleration of introduction by the electric current (NO_2 , salicylates).

IV. The theory of detoxication of poisonous ions by electrolysis is fallacious. The application of an electric current is not specific for the egress of particular ions, except those with a relatively great migrational velocity (*i. e.*, H, Na, Cl_2 , I_2). The migrational velocity of the ions of the common poisons, as the heavy metals and alkaloids, is very small as compared to that of the ions normally present in the tissue, and therefore the principle of detoxication cannot be applied to the former.

V. After the administration of iodides, per os or subcutaneously, nascent iodine can be liberated within the tissues by the insertion of a positive pole of an electrode. This principle may possibly be utilized in the treatment of certain infections. However, equally beneficial effects seem to be obtainable by the application of the electric current *per se*, as a result of the drastic tissue changes which are produced.

BIBLIOGRAPHY.

1. Alt and Schmidt: *Electricity in Medicine*, W. H. Guillemnot, p. 201.
2. LeBlanc, M.: *A Text-book of Electrochemistry*, The MacMillan Company, New York, p. 59.
3. Fette, G. T.: *Jour. Nat'l Dental Assn.*, 1918, 5, 1033.
4. Inchley, O.: *Jour. Pharm. and Exp. Therap.*, 1921, 18, 241.
5. Cross, H. V.: *Arch. Radiol. and Electro.*, 1918-1919, 23, 149.
6. Rolfe, W. A.: *Boston Med. and Surg. Jour.*, 1919, 181, 196.
7. Fowler: *British Med. Jour.*, 1913, 1, 922.
8. Clark, W.: *Am. Jour. Electrotherap. and Radiol.*, 1919, 27, 98.
9. Turrell, W. J.: *Arch. Radiol. and Electro.*, 1922, 27, 130.
10. Turrell, W. J.: *Am. Jour. Electrotherap. and Radiol.*, 1920, 38, 229.
11. Friel, A. R.: *Practitioner*, London, 1918, 101, 315.
12. Friel, A. R.: *Lancet*, 1920, 199, 345.
13. Borrel, A., de Coulon, M., and Boez, L.: *Compt. rend. soc. de biol.*, Paris, 1922, 87, 1118.
14. Wardle, M.: *British Med. Jour.*, 1919, 2, 495.
15. Jacoby, G. W.: *A System of Physiological Therapeutics* (edited by S. S. Cohen), Vol. II, *Electrotherapy*, P. Blakiston's Sons & Co., Philadelphia, 1902.
16. Bourguignon, G.: *Arch. Radiol. and Electro.*, 1922, 27, 139.
17. Harris, J. D.: *Arch. Radiol. and Electro.*, 1920, 23, 222.

STUDIES IN PANCREATIC FUNCTION. THE ENZYMIC CONCENTRATIONS OF DUODENAL CONTENTS IN HEALTH AND DISEASE.*

By C. W. McCLURE, M.D.

WITH THE COLLABORATION OF

CHESTER M. JONES, M.D., A. S. WETMORE,

AND

LAWRENCE REYNOLDS, M.D.

(From the Evans Memorial, Boston, Mass.)

THE present communication deals with the principal results obtained from a study of the enzymic concentration of duodenal contents. The contents were derived from normal persons and those with pathological affections of the pancreas, liver or gastro-intestinal tract. The main purpose of the study was to devise methods for demonstrating the degree of activity of the external secretory function of the pancreas, and to apply those methods to the investigation of this function in various pathological conditions involving the gastro-intestinal tract, including the liver and pancreas.

Physicians are, naturally, most interested in that phase of laboratory investigation which develops methods which can be applied clinically. The development of such an investigation is very apt

* Presented, by invitation, to the American Gastro-enterological Association, Atlantic City, 1923.

to divide itself into the following three stages: (1) Devising of methods suitable for pursuing the problem; (2) application of the methods to the study of normal man; and (3) their application to the study of pathological conditions. These stages of development are exemplified by the present investigation.

Enzymic concentration was determined by estimating the activities of the proteolytic, lipolytic, and amylolytic enzymes of duodenal contents which were active in alkaline media. The methods used have already been presented in the *Archives of Internal Medicine*¹ and the *Journal of the American Medical Association*.² Proteolytic activity is estimated by allowing duodenal contents to act on a solution of casein. The casein not affected by the proteolytic enzyme is precipitated by means of metaphosphoric acid solution. The index of proteolytic concentration is taken as the number of milligrams of non-protein nitrogen left in solution by the metaphosphoric acid. This nitrogen is determined by an adaptation of the methods of Folin and Wu for the determination of non-protein nitrogen in the blood. Amylolytic activity is estimated as the number of milligrams of glucose developed by the action of a standard quantity of duodenal contents on a solution of soluble starch. The index of amylolytic concentration is taken to be the total number of milligrams of glucose developed, as estimated by the method of Folin and Wu for the determination of sugar in the blood. Lipolytic activity is estimated by allowing duodenal contents to act on a true emulsion of cottonseed oil and determining the amount of acidity developed by titrating with $N/10$ alcoholic NaOH solution. The total number of cc of $N/10$ NaOH necessary to neutralize the acidity developed is used as the index of lipolytic concentration. The duodenal contents and the reagents used must be controlled for the presence of nitrogen not precipitated by the metaphosphoric acid, for copper reducing bodies and for acidity.

The reason for the development of the methods described have been discussed in a previous communication.¹ For this reason it will suffice to state that the chemistry of all other methods is so grossly erroneous as to render the interpretation of results obtained by them well-nigh impossible.

Duodenal contents were obtained by use of the gastro-duodenal tube. The metal tip was allowed to pass through the pyloric sphincter and as far as the proximal end of the second portion of the duodenum. The position of the tube was ascertained by fluoroscopic observations. The subjects then reclined on the right side and the contents were obtained by siphonage.

Having devised methods, the next step was to apply them to the study of normal persons. The first study made on normal persons was that of the enzymic concentrations of duodenal contents collected while the stomach was in the fasting state. Duodenal contents collected under this condition showed marked variation in the

concentration of the various types of enzymes. These variations were found in specimens from the different subjects and in different specimens from the same subject. The findings are exemplified by those in the specimens of duodenal contents from two subjects which are outlined in the following table.

TABLE I.—ENZYMIC CONCENTRATIONS, AMOUNTS AND PHYSICAL CHARACTER OF FASTING-DUODENAL CONTENTS COLLECTED OVER THIRTY-MINUTE PERIODS

Subject.	Enzymic concentration.			Amount in cc.	Color.	Viscosity.
	Proteolytic in mg. NPN.	Lipolytic in cc N/10 NaOH.	Amylolytic in mg. glucose.			
C. . . .	2.4	2.7	1.4	50	Pale greenish	Slight.
	1.2	0.4	0.6	135	Light brown	Moderate.
	1.8	0.5	0.3	15	Lemon-yellow	Slight.
	1.6	0.5	0.3	15	Lemon-yellow	Moderate.
	4.3	1.0	0.8	60	Lemon-yellow	Slight.
F. . . .	2.5	0.4	1.6	58	Pale yellow	Slight.
	0.6	0.6	2.1	40	Pale greenish	Slight.

Although the fasting stomach contained no liquid or food ingested by the subjects, nevertheless in taking the tube subjects also swallowed much saliva. It is also well known that the fasting stomach contains more or less acid secretion, cellular débris and mucin. Undoubtedly, the stomach throws these materials over into the duodenum, so that a truly fasting state of the stomach and duodenum is not obtainable. Just what role the presence of these materials in the duodenum played in the production of the presence of enzymes in the duodenal contents was not determined. However, this does not detract from the accuracy of the observations, which were made on 22 different specimens of duodenal contents obtained from 6 normal persons. The amounts of these specimens varied from 29 to 135 cc, the color was some shade of pale yellow and the viscosity varied from slight to moderate. Proteolytic concentration varied from 1.2 to 5.0 mgs. of non-protein nitrogen, lipolytic concentration from 0.0 to 2.7 cc of NaOH, and amylolytic concentration from 0.3 to 6.7 mgs. of glucose.

A study was made of the effect of the ingestion of moderate sized meals on the enzymic concentration of duodenal contents. For this purpose a semi-solid meal of milk and cottage cheese, representing a mixed diet of protein, fat and carbohydrate, was used. The volume of the meal was 300 cc. It took about four hours for the stomach to empty itself of the meal, during which time duodenal contents were collected over hourly periods. The enzymic con-

centrations of the different hourly specimens were comparable; in other words, the concentrations did not show systematic increase from the first to the fourth hours. These findings demonstrated that hourly collections of duodenal contents contained enzymic concentrations representative of those occurring throughout the period of gastric digestion; *i. e.*, the time during which the stomach was emptying itself of food.

Further observation showed that an hourly specimen of duodenal contents derived from a meal of a volume of 50 cc contained enzymic concentrations comparable to those obtained by the use of meals of a volume of 300 cc. But comparable results could be obtained only if the collection time of the duodenal contents was proper, as will be described later on. The use of meals of small volume was practical both from the standpoint of the comfort of the subject and in lessening the laboratory work. For these reasons all the work which will be subsequently described was carried out with the meals of a volume of 50 cc.

The next studies were made on the effect of single pure food substances on the enzymic concentrations of duodenal contents. The food substances used were casein, edestin, olive oil, and arrow-root starch. Usually 10 or 25 gms. of one of these, or in the later experiments of mixtures of them, were made up to a volume of 50 cc with tap water and ingested by the subject. After its ingestion the food substance appeared in the duodenal contents either immediately or within a period of twenty minutes. Other than for the presence of this food stuff no apparent change occurred in the character of the duodenal contents and no increase in the enzymic concentrations, until the lapse of periods varying from ten to forty-five minutes. The change which then occurred was most striking and consisted of an abrupt change from a pale yellow color to some shade of dark brown or a very dark yellow. Coincident with the change in color the viscosity increased and, also, the enzymic concentrations. This was shown by study of the enzymic concentrations of fractions of duodenal contents collected over periods of fifteen minutes up to and during the hour succeeding the change to the dark colored bile. The enzymic concentrations of duodenal contents collected during this hour were found to be comparable to those collected over hourly periods after the ingestion of meals of a volume of 300 cc. During a part, at least, of this hour the food substance which had been ingested was passing out of the stomach and through the duodenum. However, the emptying time of the stomach was found to vary; sometimes the stomach emptied itself of the food substance in about an hour, while in other instances there would be a residue remaining at the end of two hours. When the emptying time of the stomach extended well into the second hour the enzymic concentrations of the duodenal contents were comparable to those collected during the first hour.

But if the stomach emptied during the period of the first hour of collection, the duodenal contents obtained during the second hour showed enzymic concentrations comparable to those obtained under fasting conditions. The time coincidence of the onset of the flow of bile and pancreatic juice suggests a common stimulant.

TABLE II.—ENZYMIC CONCENTRATIONS, AMOUNTS AND PHYSICAL CHARACTER OF DUODENAL CONTENTS COLLECTED OVER PERIODS I, II AND III.*

Subject.	Enzymic concentration.			Amount in cc.	Color.	Viscosity.	Kind of food ingested.	Period of collection.
	Proteolytic in mg. NPN.	Lipolytic in cc N/10 NaOH.	Amylolytic in mg. glucose.					
C. . .	3.9	2.3	1.4	30	Pale yellow	Slight	None	I
	0.0	0.2	0.0	50	Light yellow	Slight	Casein	II
	4.2	2.0	1.0	165	Very dark yellow	Moderate	Casein	III
F. . .	1.4	0.6	2.1	50	Light yellow	Slight	None	I
	0.8	0.3	1.2	40	Light yellow	Slight	Olive oil	II
	5.6	4.4	3.0	100	Dark brown	Moderate	Olive oil	III

* Period I, while the stomach was fasting; Period II, from immediately after the ingestion of food until the abrupt change to a dark-colored bile occurred; Period III, during the first hour after the abrupt change to dark-colored bile occurred.

Table II gives figures representing the concentrations of the three types of pancreatic enzymes in duodenal contents collected over the following periods: (I) While the stomach was fasting; (II) from immediately after the ingestion of a food substance until the abrupt change to a dark-colored bile occurred; (III) during the first hour after the change to dark-colored bile occurred. Study of the figures in Table II for the first two periods of collection shows that the concentrations of the various types of enzymes varied from very little to relatively great. On the other hand, it will be noted that none of the figures representing the enzymic concentrations of the third period of collection are less than whole numerals. This difference in magnitude of the minimum variations in enzymic concentrations sharply differentiates this one period from all others; and is well demonstrated in Table III.

Study of Table III demonstrated that fasting duodenal contents occasionally showed enzymic concentrations apparently comparable to those found in contents obtained during the third period of collection. But the fasting contents were relatively undiluted, while those collected after the ingestion of food were diluted with bile and gastric chyme. Amounts of the latter were particularly large after the ingestion of meals of a volume of 300 cc as judged both by the quantities of duodenal contents collected and the amounts

of barium seen to be ejected from the stomach into the duodenum when observed through the fluoroscope. For this reason the enzymic concentrations found in duodenal contents during the time the stomach was emptying itself of food represented greater concentrations of enzymes than were present in fasting duodenal contents. As has been stated, the enzymic concentrations of this third period of collection, after the ingestion of a meal of 50 cc volume, were comparable to those found in duodenal contents derived from meals of a volume of 300 cc. From these findings it is concluded that the presence of food in the stomach and duodenum in some way brings about the stimulation of the secretion of pancreatic juice, and that this stimulation is represented by an increase in the enzymic concentrations of duodenal contents collected during the third period of collection, as represented in Table III.

TABLE III.—MINIMUM AND MAXIMUM DEGREES OF ENZYMIC CONCENTRATIONS OF DUODENAL CONTENTS COLLECTED OVER PERIODS I, II AND III.*

Period of collection.	Enzymic concentrations.					
	Proteolytic in mg. NPN.		Lipolytic in cc N/10 NaOH.		Amylolytic in mg. of glucose.	
	Minimum.	Maximum.	Minimum.	Maximum.	Minimum.	Maximum.
Period I	1.2	5.0	0.0	2.7	0.3	0.7
	0.8	4.3	0.0	2.2	0.0	3.1
	2.7	5.7	1.0	4.4	2.5	4.5

* Period I, while the stomach was fasting; Period II, from immediately after the ingestion of food until the abrupt change to a dark-colored bile occurred; Period III, during the first hour after the abrupt change to dark-colored bile occurred.

The enzymes whose concentrations have been studied may be derived from sources other than the pancreas; *i. e.*, the stomach, duodenal mucosa and saliva. It is conceivable that ptyalin might reach the duodenum in active form; such an occurrence would increase the amylolytic concentration. Gastric lipase, if such an entity exists, would be present in negligible amount, judging from the small quantity said to be demonstrable in stomach contents; while pepsin is not active in the hydrogen-ion concentration used in the method for demonstrating proteolytic activity. While certain enzymes are demonstrable in the duodenal mucosa, their presence in the lumen of the gut has never been shown. Furthermore, diminution in enzymic concentrations was found under conditions which depressed pancreatic function, as will be demonstrated later on in this article. For these reasons it may be assumed that the concentrations of enzymes demonstrated by the methods used

in this investigation represented, very largely at least, enzymes secreted by the pancreas.

The work so far discussed has described the development of the procedures which gave results showing the effects of food on the enzymic concentrations of duodenal contents. The next step was to determine the comparative effects on enzymic concentrations of specific types of food substances. For this study 5 normal subjects were fed casein, edestin, olive oil or arrowroot starch. Each feeding experiment was done on a different day. The food substances were fed in 10-gm. amounts to 2 subjects and in 25-gm. amounts to three. The results are outlined in the following table (Table IV).

TABLE IV.—ENZYMIC CONCENTRATIONS AND PHYSICAL CHARACTER OF DUODENAL CONTENTS DERIVED FROM PURE FOOD SUBSTANCES, FED SINGLY AND IN COMBINATIONS.

Subject.	Enzymic concentrations.			Color.	Viscosity.	Kind of food ingested.
	Proteo-lytic in mg. NPN.	Lipo-lytic in cc N/10 NaOH.	Amylo-lytic in mg. glucose.			
A.	3.9	2.4	4.5	Dark brown	Moderate	Olive oil, 10 cc.
	3.3	1.8	2.4	Brownish-yellow	Moderate	Edestin, 10 gm.
	2.4	1.4	2.5	Yellowish-brown	Moderate	Arrowroot starch, 10 gm.
	4.7	2.0	3.5	Dark-yellow brown	Moderate	Olive oil, 5 cc; edestin, 5 gm.
	5.0	0.7	2.9	Yellowish-brown	Moderate	Olive oil, 5.3 cc; edestin, 5.3 gm.; starch, 5.3 gm.
B.	3.2	1.8	3.6	Very dark brown	Moderate	Olive oil, 10 cc.
	3.4	1.5	3.6	Dark brownish-yellow	Moderate	Edestin, 10 gm.
	3.0	1.0	3.3	Yellowish-brown	Moderate	Arrowroot starch, 10 gm.
	3.4	1.2	3.1	Brownish-yellow	Moderate	Arrowroot starch, 5 gm.; olive oil, 5 cc.
	4.3	0.0	2.7	Brownish-yellow	Moderate	Edestin, 5 gm.; arrowroot starch, 5 gm.
C.	2.1	0.8	2.1	Yellow	Moderate	Casein, 25 gm.
	4.2	2.0	1.0	Blackish	Moderate	Olive oil, 25 cc.
D.	5.7	3.5	2.6	Yellow	Moderate	Casein, 25 gm.
	3.5	1.4	3.5	Blackish	Moderate	Olive oil, 25 cc.
E.	3.5	3.3	4.3	Yellow	Moderate	Casein, 25 gm.
	4.9	3.2	1.4	Blackish	Moderate	Olive oil, 25 cc.
F.	6.0	4.80	4.3	Yellow	Moderate	Casein, 25 gm.
	5.6	4.4	3.0	Blackish	Moderate	Olive oil, 25 cc.

Study of Table IV shows that the concentration of lipase was greatest after the ingestion of olive oil, less after edestin or casein

and least after the ingestion of starch; in 2 of the subjects the food mixtures yielded duodenal contents showing still lower lipolytic concentration. These findings demonstrate a relationship between the kind of food ingested and the enzymic concentrations of duodenal contents.

Having established the effects of food on the enzymic concentrations of duodenal contents the next step in the investigation was to ascertain the effects of water drinking. For this purpose the fasting contents were collected for thirty minutes, then the subject was given 50 cc of tap water and the contents again collected for periods of forty-five minutes to one hour. In certain of the experiments the contents were collected over the period of a second hour. The enzymic concentrations found in the contents collected during the second hour were fully comparable to those obtained during the first hour. Experiments were carried out on 5 normal persons, and results obtained are exemplified in the following representative table (Table V). To this table are added figures representing the enzymic concentrations of duodenal contents derived from olive oil or edestin.

TABLE V.—ENZYMIC CONCENTRATIONS AND AMOUNTS OF DUODENAL CONTENTS COLLECTED FROM THE FASTING DUODENUM AND AFTER THE INGESTION OF TAP WATER, OLIVE OIL, EDESTIN OR CASEIN.

Subject.	Enzymic concentrations.			Amount in cc.	Duration of collection in minutes.	Kind of food ingested.
	Proteolytic in mg. NPN.	Lipolytic in cc N/10 NaOH.	Amylolytic in mg. glucose.			
C. . . .	1.8	0.5	0.3	30	30	Fasting duodenum.
	1.5	0.1	0.0	52	45	Tap water, 50 cc.
	4.2	2.0	1.0	165	60	Casein, 25 gm.; tap water, 25 cc.
	5.7	3.5	2.6	100	60	Olive oil, 25 cc; tap water, 25 cc.
B. . . .	1.9	1.1	1.8	25	30	Fasting duodenum.
	3.0	0.5	2.0	60	60	Tap water, 50 cc.
	2.7	1.5	2.5	140	60	Edestin, 10 gm.; tap water, 40 cc.
	3.2	1.8	3.6	270	60	Olive oil, 10 cc; tap water, 40 cc.

As the above table shows, enzymic concentrations were diminished in some cases after the ingestion of water, possibly by dilution. On the other hand, the concentration of one type of enzyme might be increased, while that of the other types remained approximately the same or was diminished; the resultant figures expressing enzymic concentration were comparable to those obtained for fasting con-

tents. The table, also, shows that the enzymic concentrations of duodenal contents were much greater after the ingestion of food than after water. These findings demonstrate very definitely that water was a less potent stimulant to the secretion of pancreatic juice than was food. They present further evidence that the enzymic concentrations of duodenal contents were influenced by the kind of material ingested.

Studies of the hydrogen-ion concentration of duodenal contents were made after the ingestion of meals of 300 cc and of 50 cc volume. The large meals were composed of milk and cottage cheese or of 20 per cent cream; the small meals were of olive oil or edestin. The hydrogen-ion concentration was found to vary from 3 to 8; and no relation was found to exist between the degrees of acidity and the magnitude of enzymic concentrations. In fact, the duodenal contents from the cream or olive oil were often alkaline; but, nevertheless, showed as a rule, enzymic concentrations greater than were found in acid contents derived from protein or carbohydrate meals.

The findings which have been discussed in the present investigation are of interest in relation to the various theories concerning the mechanism by which the external secretory activity of the pancreas is stimulated.

As has been discussed, evidence of pancreatic stimulation was much less pronounced after the drinking of water than after the ingestion of foodstuffs. This finding occurred in spite of the fact that water stimulates the secretion of acid gastric juice; so that after its ingestion acid fluid was ejected from the stomach into the duodenum. From this it is concluded that something more than the mere ejection of acid contents into the duodenum is necessary to stimulate materially pancreatic secretion. It was also demonstrated that a relation existed between the degrees of enzymic concentration and the kind of foodstuff ingested; while on the other hand, no relation was found between the magnitude of enzymic concentration and the degree of acidity of the duodenal contents. The findings, therefore, present evidence that the acidity of duodenal contents is not the essential factor causing the stimulation of pancreatic juice in man.

It will be recalled that, after the ingestion of food and its appearance in the duodenal contents, a period existed during which digestion and absorption of the digested products could occur. Therefore, the finding: (1) That food in some way stimulated the secretion of pancreatic juice; (2) that a relation existed between the degrees of enzymic concentration and the kinds of food ingested; (3) that a latent period existed in which the foodstuffs could be digested and absorbed; and (4) that water was a much less potent pancreatic stimulant than food, although water stimulates a normal gastric acidity, present evidence that the products of food digestion are an essential factor in stimulating the secretion of pancreatic juice.

The above interpretation of the findings in the experimental work here reported do not agree with the view of Pawlow,⁴ except for lipolytic activity. They do not uphold either the secretin theory of Bayliss and Starling⁵ nor the hypothesis of a nervous mechanism as the most potent factors in the stimulation of pancreatic juice. The remaining most probable possibility is that the products of the digestion of food are the essential factor in stimulating the pancreas to secretory activity in man.

The disagreement with Pawlow's contentions may possibly be more apparent than real. In the first place Pawlow worked on dogs; and a pancreatic regulatory apparatus may exist in dogs which is different from that of man. In the methods used by Pawlow for demonstrating enzymatic activity the substrates acted upon by enzymes were placed directly into the pancreatic juice. The hydrogen-ion and buffer conditions of the various specimens of pancreatic juice may have been such as to give results justifying Pawlow's conclusions. But the physical chemistry of Pawlow's methods is so grossly erroneous that an interpretation of results by them is well-nigh impossible.

The experiments of Bayliss and Starling⁵ consisted in the intravenous injection into animals of hydrochloric acid extracts of duodenal mucosa. In this way pancreatic secretion was stimulated. But the work of von Fürth⁶ clearly demonstrates that it is not necessary to assume the existence of "secretin" to explain this stimulation. This investigator, among others, has demonstrated that various well-known chemical substances normally present in duodenal mucosa will produce such a stimulation. Furthermore, the maceration of duodenal mucosa and its extraction with hydrochloric acid might very well form compounds (due to decomposition of proteins, etc.) similar to those occurring during digestion; such compounds may play a role in the stimulation of pancreatic juice when injected into the blood-stream of an animal. In other words, the chemistry of the work of Bayliss and Starling was such as not to justify the drawing of far-reaching conclusions from their observations.

Experiments have been repeatedly carried out by the present authors in which water, N_{20} HCl, glucose solutions and olive oil have been introduced directly into the duodenum of men. The results were the same as those obtained after the ingestion of these substances by mouth. Certainly these substances were introduced in an inert chemical state, except the N_{20} HCl. This contradicts the often-quoted statement that such substances do not stimulate pancreatic secretion. From these experiments it was concluded that whenever any harmless liquid is introduced into the duodenum of man, intestinal digestion and absorption may begin.

The absorption of materials present in the duodenal contents and those coming into the duodenum from the stomach, for in

man the introduction of fluid into the duodenum always starts up the ejection of stomach contents into the duodenum as the authors have repeatedly demonstrated, could explain the often quoted experiment of Popielski.⁷ In this experiment hydrochloric acid solution was placed in the duodenum of one dog, whose blood supply was connected to that of another dog; as a result pancreatic juice was secreted by the latter. The contamination of the original duodenal material with gastric contents introduces an element of uncertainty, as digestible material thus present would give rise to products analogous to those produced by food digestion. In fact all the work supporting the "secretin" theory furnishes only indirect evidence of the correctness of that theory; while phenomena urged in its support can all be explained in other ways.

This discussion is not intended to belittle the excellent work of two such competent experimenters as Drs. Bayliss and Starling. But the purpose is to emphasize that "secretin" remains a hypothetical substance. Furthermore, it should be emphasized that the work on "secretin" has all been carried out on the lower animals; and whether or not the same experimental results would be obtained in man has not been determined.

The next phase of the investigation deals with the enzymic concentration of duodenal contents in diseased conditions of the pancreas, liver and gastro-intestinal tract.⁸ Under such conditions bile was frequently not present in the duodenal contents. As a result, the criteria previously used for the time of beginning the collection of duodenal contents suitable for enzymic concentration studies were absent. Because of this it was necessary to find a type of meal that would stimulate the flow of pancreatic juice within a few minutes after its entrance in the duodenum. This was accomplished by a meal consisting of 50 cc of 20 per cent cream, containing 15 grams of barium sulphate. The addition of barium sulphate allowed the behavior of the meal to be observed through the fluoroscope and it, also, frequently hastened the time of ejection from the stomach into the duodenum. The latter result was apparently a mechanical one, brought about in that the weight of the barium aided in getting the cream quickly into the pyloric region of the stomach.

The technic used in obtaining duodenal contents from pathological subjects is as follows: The duodenal tube was allowed to enter the second portion of the duodenum. The subject then ingested the meal described and reclined on the right side. The flow of duodenal contents was initiated by gentle aspiration with a syringe and as soon as cream and barium were obtained the collection was begun. The period of collection was one hour.

The minimum figures for the enzymic concentrations of duodenal contents derived from normal persons, after the ingestion of the meal and cream, were as follows: Proteolytic, 2 mgs. non-protein

nitrogen; lipolytic, 1 cc N_{10} NaOH; and amylolytic, 1 mg. of glucose. The figures were the minimum figures, also, for enzymic concentrations of duodenal contents derived from patients with a variety of non-febrile diseases, and in whom there was no reason to suspect pancreatic involvement.

Among the pathological conditions studied were cases of diabetes mellitus, pernicious anemia, and achylia gastrica. The findings of normal enzymic concentrations in these cases are of both pathological and physiological interest. From the clinical standpoint, they exclude non-pancreatic conditions as factors affecting the enzymic concentrations of duodenal contents. Physiologically, the findings in achylia gastrica bear on the question of the secretin theory. In spite of the fact that in the cases studied, Toepfer's reagent failed to demonstrate the presence of hydrochloric acid in the gastric secretions, normal enzymic pancreatic function was found. This finding indicates that hydrochloric acid is not an essential factor in stimulating the secretion of pancreatic juice in man.

Study was made of the enzymic concentration of duodenal contents from patients in whom organic pancreatic disease was demonstrated at laparotomy or autopsy. The concentrations found fall into three classes, as follows: (1) Normal; (2) abnormally low; and (3) an intermediate value between those two.

1. Normal concentration was found in acute or chronic destructive lesions which did not involve the head of the pancreas; for example, destruction of the body and tail of the pancreas by cancer, but without involvement of the head of the organ.

2. Abnormally low concentrations were found in two types of conditions as follows: Destructive lesions involving the head of the pancreas, such as cancer of the head of the pancreas or acute pancreatic necrosis; and chronic pancreatitis with or without extensive involvement of the glandular parenchyma.

3. The intermediate value between normal and abnormally low concentrations was characterized by normal concentration of one or two enzymes while the other one or two was much diminished below the minimum normal; *i. e.*, dissociation of the concentrations of the various types of enzymes occurred. This was found in the duodenal contents of patients convalescing from acute pancreatic necrosis. Findings representative of these described are outlined in the table on page 661.

In studying patients with disease of the biliary tract the duodenal enzymic concentrations were found to fall into the same three classes described for pancreatic diseases; *i. e.*, normal, abnormally low, and intermediate or dissociated.

Normal concentrations of duodenal enzymes were found where no obstruction to the pancreatic duct existed. The concentrations were apparently not affected by the presence of bile or by its partial or complete absence in the duodenal contents. The patients studied were those with cancer of the bile ducts and partial or

complete obstruction of the common duct due to stone, the pancreatic duct not being affected. Three of the patients had been diagnosed clinically as cancer of the head of the pancreas. In the duodenal contents from 1 of these patients no bile pigment was observed; while the contents from the other 2 were pale green in color. The findings of normal enzymic concentrations in these cases cast doubt on the diagnosis of pancreatic malignancy, and on laparotomy stone in the common duct was found in each case.

TABLE VI.—ENZYMIC CONCENTRATIONS, AMOUNTS AND PHYSICAL CHARACTER OF DUODENAL CONTENTS OBTAINED FROM PATIENTS WITH DISEASE OF THE PANCREAS.

Subject.	Enzymic concentration.			Amount in cc.	Color.	Viscosity.	Diagnosis.
	Proteolytic in mg. NPN.	Lipolytic in cc. N/10 NaOH.	Amylolytic in mg. glucose.				
1x . . .	2.5	1.6	2.0	90	Greenish-yellow	Moderate	Cancer body and tail pancreas.
2x . . .	0.0	0.2	2.0	55	White	Great	Cancer head of pancreas.
3x . . .	0.8	0.3	0.3	50	Yellow	Moderate	Chronic pancreatitis.
	1.1	0.3	0.5	60	Yellow	Moderate	
4x . . .	1.9	0.7	1.9	150	Yellow	Moderate	Acute pancreatitis; convalescing.
	5.0	0.2	0.4	100	Yellow	Moderate	

x, Exploratory laparotomy.

Abnormally low and dissociated concentrations were found when the lesion obstructing the common duct involved the pancreatic duct also. With one exception, this lesion was stone in the ampulla of Vater. The exception noted was one in which sclerotic processes almost occluded the common bile duct.

Three of the cases studied are worthy of special mention. In these cases calculi obstructed the ampulla of Vater, and on the first examination the duodenal enzymic concentrations were much below the normal; while no bile was seen in the duodenal contents from 2 of the cases, and from the third were a pale green color. After lavage with magnesium sulphate solution a few times the duodenal contents showed bile pigment and normal enzymic concentrations. On the other hand, in 4 cases of cancer involving the bile ducts repeated lavage of the duodenum failed to be followed by bile in the duodenal contents. Two of the cases represented cancer of the head of the pancreas involving the pancreatic duct and lavage did not produce a change in the abnormally low enzymic concentrations. In the other 2 the pancreatic duct was not involved and the enzymic concentrations were normal. In these cases the use of magnesium sulphate lavage, combined with study of enzymic con-

centrations, of the duodenal contents gave findings in the presence of benign obstruction which were different from those obtained when the obstruction was of malignant character. The differences were so marked as to suggest that results obtained from the combined use of duodenal lavage and enzymic concentration studies will prove to be of value in differentiating between the two types of obstruction.

In obstructive jaundice the question frequently arises as to whether the cause is benign or malignant. The three most frequent malignant diseases causing jaundice are primary cancer of the head of the pancreas, primary cancer of the bile ducts, and cancer of the liver secondary to gastric carcinoma. The latter can almost invariably be demonstrated by Roentgen-ray examination of the stomach; cancer of the bile ducts does not allow bile to flow into the duodenum; and cancer of the head of the pancreas will usually occlude the pancreatic duct and largely exclude enzymes from the duodenum. Thus the estimation of duodenal enzymic concentrations would seem to be of distinct value in the diagnosis of a suspected cancer of the biliary tract or of the head of the pancreas.

The findings in biliary disease, which have been discussed, are exemplified in the following table (Table VII)

TABLE VII.—ENZYMIC CONCENTRATIONS, AMOUNTS AND PHYSICAL CHARACTER OF DUODENAL CONTENTS OBTAINED FROM PATIENTS WITH DISEASE OF THE BILIARY TRACT.

Subject.	Enzymic concentration.			Amount in cc.	Color.	Viscosity.	Diagnosis.
	Proteolytic in mg. NPN.	Lipolytic in cc x/10 NaOH.	Amylolytic in mg. glucose.				
1x . .	9.0	4.0	2.0	150	Yellow	Moderate	Cholelithiasis; no obstruction.
2x . .	2.7	1.6	0.7	100	Pale yellow	Great	Stone in common duct; deep icterus.
3x . .	2.0	0.2	0.6	50	White	Great	Stone in ampulla; deep icterus.
	3.9	1.0	0.9	70	Pale yellow	Moderate	After lavage with MgSO ₄ .
4x . .	1.0	0.1	0.0	150	White	Great	Stone in ampulla; deep icterus.
	5.9	1.9	3.3	100	Greenish-yellow	Moderate	After lavage with MgSO ₄ .

x, Laparotomy.

The effects of biliary and pancreatic diseases on the enzymic concentrations of duodenal contents, which have been discussed, may be summarized as follows:

(a) Abnormal enzymic concentrations were found in lesions

obstructing the pancreatic duct or causing extensive damage to the head of the pancreas. The lesions studied were acute pancreatitis, cancer of the head of the pancreas, and obstruction to the pancreatic duct by gall stones or by sclerotic processes.

(b) Abnormal enzymic concentrations were also found in chronic pancreatitis in which there was but little destruction of the glandular parenchyma.

(c) Normal enzymic concentrations were found when the lesion involved but little of the glandular parenchyma, when the pancreatic duct was not obstructed, and when the cause for an obstructive jaundice did not involve the pancreas or its duct.

The question arises as to the need for the rather complicated and time-consuming processes of obtaining and of estimating the enzymic concentrations of duodenal contents. It has been urged that any secretory anomalies of the pancreas would be reflected in the stools, and that the examination of the stools would suffice. That such is not necessarily the case is evidenced by the findings in a case of chronic pancreatitis, in which careful stool examinations were made on successive days following a Schmidt test diet. All examinations were negative. In several of the other cases studied the stool examinations on house diet showed no evidences of abnormal digestion. In cases with a low sugar tolerance, furthermore, it is obviously inadvisable to feed test diets of a character satisfactory for stool examinations. Also, examination of stools will be of no aid in the diagnosis of pancreatic disease when bile is excluded from the intestines or when pathological conditions prevent the absorption of food from the small intestines. In addition, it is well known that bacteria always present in human intestines can duplicate all phases of enzymic digestion, so that it is conceivable that bacterial action alone could mask evidence of pancreatic disease as obtained from stool examination. In this connection it is of interest to note that McClure, Vincent and Pratt⁹ found that completely depancreatized dogs could often utilize a considerable percentage of fat of the food ingested. It seems clear, therefore, that pancreatic disease may not be evidenced by stool findings alone. For this reason in selected cases the use of the methods described and used in this work will be found of aid in the diagnosis and in following the progress of a given case.

Conclusions. 1. Normal enzymic concentrations of duodenal contents have been established for the methods and procedures described for estimating enzymic concentrations in duodenal contents obtained by the use of the procedures described.

2. Abnormalities in enzymic concentrations having been found only in the presence of some lesion involving the pancreas, either primarily or secondarily, it is concluded that the estimation of enzymic concentrations of duodenal contents furnishes an index to the activity of the external secretory function of the pancreas.

3. The findings in normal persons indicate that the essential

factors in stimulating the secretion of pancreatic juice are the products of digestion rather than the acidity of the gastric chyme.

4. The time coincidence of the onset of the flow of bile and pancreatic juice suggests a common stimulant.

5. The external secretory function of the pancreas, as measured by the enzymic concentration of duodenal contents, was found to be much depressed below the normal in chronic pancreatitis.

6. Acute pancreatic necrosis, cancer of the head of the pancreas, and lesions obstructing the pancreatic duct were accompanied by marked abnormalities in the enzymic concentrations of duodenal contents. Obstructive lesions caused great diminution, while acute necrosis often caused dissociation of the concentration of the enzymes.

7. In obstructive jaundice estimation of enzymic concentration of duodenal contents is of aid in localizing the site of the lesion, and in the differential diagnosis between its benign malignant character.

BIBLIOGRAPHY.

1. McClure, C. W., Wetmore, A. S., and Reynolds, L.: *Arch. Int. Med.*, 1921, **27**, 706.
2. McClure, C. W., Wetmore, A. S., and Reynolds, L.: *Jour. Am. Med. Assn.*, 1921, **87**, 1468.
3. McClure, C. W., and Wetmore, A. S.: *Boston Med. and Surg. Jour.*, 1922, **187**, 882.
4. Pawlow, I. P.: *The Work of the Digestive Glands*, London.
5. Bayliss, W. M., and Starling, E. H.: *Jour. Physiol.*, 1902, **28**, 325.
6. Von Fürth, O., and Schwartz, W. W.: *Pflüger's Arch. f. d. ges. Physiol.*, 1908, **124**, 427.
7. Popielski: *Zentralbl. f. Physiol.*, 1906, **19**, 801.
8. McClure, C. W., and Jones, C. M.: *Boston Med. and Surg. Jour.*, 1922, **187**, 909.
9. McClure, C. W., Vincent, B., and Pratt, J. H.: *Jour. Exp. Med.*, 1917, **25**, 381.

THE OCCURRENCE OF REGULAR VENTRICULAR RHYTHM WITH A RATE OF OVER FIFTY IN CASES OF AURICULAR FIBRILLATION.

By W. DOCK, M.D.,

AND

S. A. LEVINE, M.D.,

BOSTON.

(From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.)

AURICULAR fibrillation, once established in cases of organic heart disease, usually gives a constant and persisting arrhythmia. Certain drugs may restore the normal mechanism, but under the continued use of digitalis the spontaneous return of normal action is unusual. However, not infrequently the examiner notes that

"the heart action is regular" or "more regular." It is, therefore, of importance to remember that in many such cases graphic records show persisting fibrillation of the auricle. This mechanism was first described by Lewis¹ and Mackenzie;² in the former instance the ventricular rate was regular at 85 to 90 beats per minute and in the latter it was 70. Lewis³ regarded the condition as complete block and says: "In such instances the ventricular rate is relatively high, usually 40 to 50 per minute, but occasionally as high as 90 per minute, presumably because the block occurs at a high level in the *A-V* node and because the ventricle is governed by a rhythm formed in the *A-V* node."

There are numerous accounts⁴⁻¹¹ of regular ventricular rhythm in auricular fibrillation, with and without digitalis, in which the ventricular rate was below 50 per minute. Such cases are easily recognized as complete heart-block. With the more rapid rate, the actual condition is not recognized clinically, and it is important to know that in this clinic during the past ten years there have been 12 cases of auricular fibrillation studied with the electrocardiograph in which regular ventricular rhythm occurred after full doses of digitalis, with a rate between 55 and 85, the average rate being 68 per minute. During this time there were 614 cases of auricular fibrillation, 9 of which had periods of regular ventricular rhythm, with rates under 48. There were during the same time 16 cases of complete heart-block with regularly beating auricles. In 12 of the latter cases of complete heart-block, with no digitalis, the average rate was 35.8 beats per minute, while in 5 such cases treated with full doses of digitalis the average rate was 42.6. The maximum rate in the former group was 45 and in the latter, 60. In 1 case, included in both series, the rate was 34 without digitalis; six months later, following cardiac failure and continued use of digitalis, the ventricular rate was 55; the auricular rate had fallen from 115 to 90 beats per minute. This suggests that digitalis accelerates the ventricular pacemaker when there is *A-V* dissociation.

As we have seen it, regular and fairly rapid ventricular rhythm occurs in auricular fibrillation only after full doses of digitalis. It is always transient, lasting for hours or days. It may disappear and return later at a different rate, or the rate may vary from day to day. It seems to occur most often in badly damaged hearts. Half of our cases had severe mitral or aortic lesions, rheumatic in origin; 1 had syphilitic aortitis and others had myocardial failure without valve disease. Five died within one year of the time of observation.

Summary of Case Histories. CASE I.—Medical, No. 4036. Chauffeur, aged thirty-two years. Rheumatic fever at sixteen years; dyspnea for three years; orthopnea for one year; precordial

pain for two weeks. Apex in axilla; apical diastolic rumble and systolic murmur; liver slightly enlarged; legs not edematous. Discharged improved in eleven days. Diagnosis: Mitral stenosis and insufficiency.

CASE II.—No. 4727. Laborer, aged fifty-two years. Dyspnea and swelling of the legs for one year. Very large heart; liver just palpable; very slight edema of the ankles; blood-pressure, 244/170. Died in ninety-two days. Diagnosis: Chronic myocarditis, chronic nephritis and hypertension.

CASE III.—No. 5031. Butcher, aged seventy-two years. Ascites and edema of the legs for four months; orthopnea for two months. Apex in the axilla; sounds weak. Liver palpable; blood-pressure, 160/130. Died in ten months. Diagnosis: Chronic myocarditis.

CASE IV.—No. 5435. Fireman, aged sixty-five years. Orthopnea for five months; swelling of the ankles for six weeks. Heart enlarged; right hydrothorax; moist rales at the bases of the lungs; liver not felt; edema to mid-thigh; blood-pressure, 200/120. Discharged improved in twenty-eight days. Diagnosis: Chronic myocarditis and hypertension.

CASE V.—No. 5439. Housewife, aged forty years. Chorea and rheumatic fever in childhood; orthopnea for two years. Apex in axilla; apical diastolic thrill and murmur. Liver slightly enlarged ankles swollen. Died in two months. Diagnosis: Mitral stenosis and insufficiency.

CASE VI.—No. 6278. Housewife, aged forty-eight years. Rheumatic fever at twelve years; cyanotic for twelve years; dropsy for four months. Heart large; aortic systolic thrill and murmur. Liver edge at the navel; edema to the waist. Discharged improved in thirty-six days. Diagnosis: Aortic stenosis.

CASE VII.—No. 6845. Teamster, aged fifty-two years. Dyspnea for four months; orthopnea and swelling of the ankles for two months. Heart enlarged; presystolic gallop at the apex. Liver palpable, ascites and edema of the ankles. Moist rales at both bases. Discharged improved in thirty-six days. Diagnosis: Chronic myocarditis.

CASE VIII.—No. 6865. Printer, aged fifty-seven years. Dyspnea for four months; swelling of the legs and orthopnea for one month. Heart slightly enlarged; sounds faint. Rales throughout the lungs; edema of the legs and back. Died in fourteen days. Diagnosis: Chronic myocarditis.

CASE IX.—No. 6945. Housewife, aged thirty years. Rheumatic fever at thirteen years; dyspnea and precordial pain for two years; swelling of the abdomen and legs for two months. Heart slightly enlarged; diastolic rumble and presystolic murmur at the apex. Liver edge at the navel; marked ascites and edema of the legs. Died in twenty-one days. Diagnosis: Mitral stenosis and insufficiency.

CASE X.—No. 7101. Teacher, aged fifty years. Dyspnea for two months; precordial pain for one month; edema of legs for three weeks. Heart enlarged; loud systolic murmur all over precordium; short diastolic murmur at the apex; gallop rhythm. Large pulsating liver; edema of the legs and back; moist rales throughout the lungs; blood-pressure, 140/80. Discharged improved in fifty days. Diagnosis: Chronic myocarditis and aortic insufficiency.

CASE XI.—No. 13759. Stoker, aged fifty-seven years. Chancre at twenty-two years. Dyspnea for one year. Heart enlarged; loud aortic systolic and diastolic murmurs. Moderate ascites and edema of the legs; Wassermann, 4+. Discharged improved in thirty-six days. Diagnosis: Syphilitic aortitis and aortic insufficiency.

CASE XII.—No. 20712. Domestic, aged fifty-four years. Palpitation for five years; shortness of breath for two years. Night-sweats and productive cough for three weeks. Heart slightly enlarged; no murmurs; very many moist rales throughout the lungs; blood-pressure, 155/70. Discharged improved in sixty-six days. Diagnosis: Chronic myocarditis.

The records of these 12 cases were diagnosed and filed as "complete heart-block," but the rapidity of the ventricular rate was noted and an attempt made to see if this might not be better explained by another mechanism. It seemed possible that in these cases there might be a high-grade partial block, due to digitalis, with the ventricle responding, for example, to every fifth or sixth impulse originating in the auricle, and that, as in certain instances of flutter, the block might be varied by changes in vagus tone. In the 2 cases, in 1916, vagal pressure produced no change in the rate of the ventricle. It was assumed at that time that the fibrillating auricle was absolutely irregular as distinguished from the very regular rhythm of the auricle in flutter, but the work of Lewis and his co-workers,^{12, 13} on the circus movement of the auricular impulse has shown the very close analogy between the two conditions. It, therefore, seemed worth while, in reporting these cases,

to reëxamine the tracings for any evidence of similarity between the mechanism of these hearts and that of auricular flutter with a regular ventricular rhythm.

Case No.	Day in hospital.	Total amount of digitalis to date of observation.	Auricular mechanism.	Ventricular mechanism.	Ventricular rate per min.
		Grams.			
1.	1	0	Fibrillation	Irregular	100
	3	1.2	Fibrillation	Regular	73
	4	1.2	Fibrillation	Regular	73
	7	1.2	Fibrillation	Regular	57
2.	1	0	Fibrillation	Irregular	80
	58	4.5	Fibrillation	Irregular	90
	65	5.05	Fibrillation	Regular	81
	75	5.05	Fibrillation	Irregular	68
3.	1-7	0-2.45	Flutter	Varying block	100-130
	8 A.M.	0-2.45	Fibrillation	Irregular	52
	8 P.M.	2.65	Fibrillation	Regular	60
	9-20	2.65	Fibrillation	Irregular	48-62
	20-29	2.65-7.05	Flutter	Varying block	80-140
	30	7.15	Fibrillation	Regular	42
	31-38	7.15	Fibrillation	Irregular	39-60
	39	7.15	Regular	Regular	85
4.	1	Tincture to nausea	Fibrillation	Regular	85
	4-9	0.40-0.75	Fibrillation	Coupled	68-76
	11-21	0.75-1.55	Fibrillation	Irregular	54-61
5.	1-7	0.1	Fibrillation	Irregular	125-90
	10	1.7	Fibrillation	Regular	66
	26	2.8	Fibrillation	Irregular	90
6.	1	Digalen, gtts. v b.d. (2 mos.)	Fibrillation	Regular	58
	6	Digalen, gtts. v b.d. (2 mos.)	Fibrillation	Irregular	45
7.	1	0	Fibrillation	Irregular	150
	4	2.5	Fibrillation	Irregular	80
	6	2.5	Fibrillation	Regular	88
	26-36	2.5-3.4	Fibrillation	Irregular	83-90
8.	3	2.1	Fibrillation	Regular	56
	5-9	2.1	Fibrillation	Irregular	85-105
9.	1	0	Regular	Regular	108
	6	1.3	Regular	Dropped beats	80
	7	1.3	Fibrillation	Regular	68
	8-9	1.3	Fibrillation	Irregular	70-75
	15	2	Fibrillation	Coupled	94
10.	3	0.9	Fibrillation	Irregular	75
	7	2.1	Fibrillation	Regular	75
	21 A.M.	2.9	Fibrillation	Irregular	72
	21 P.M.	2.9	Fibrillation	Regular	75
11.	3	0	Regular	Regular	90
	7	3.0	Fibrillation	Regular	58
	11	3.0	Regular	Dropped beats	65
	22	3.0	Regular	Regular	88
12.	1	0	Fibrillation	Irregular	155
	3	1.6	Fibrillation	Irregular	65
	22	3.85	Fibrillation	Regular	59
	28	4.45	Fibrillation	Regular	58
	31-66	4.45-6.0	Fibrillation	Irregular	50-70

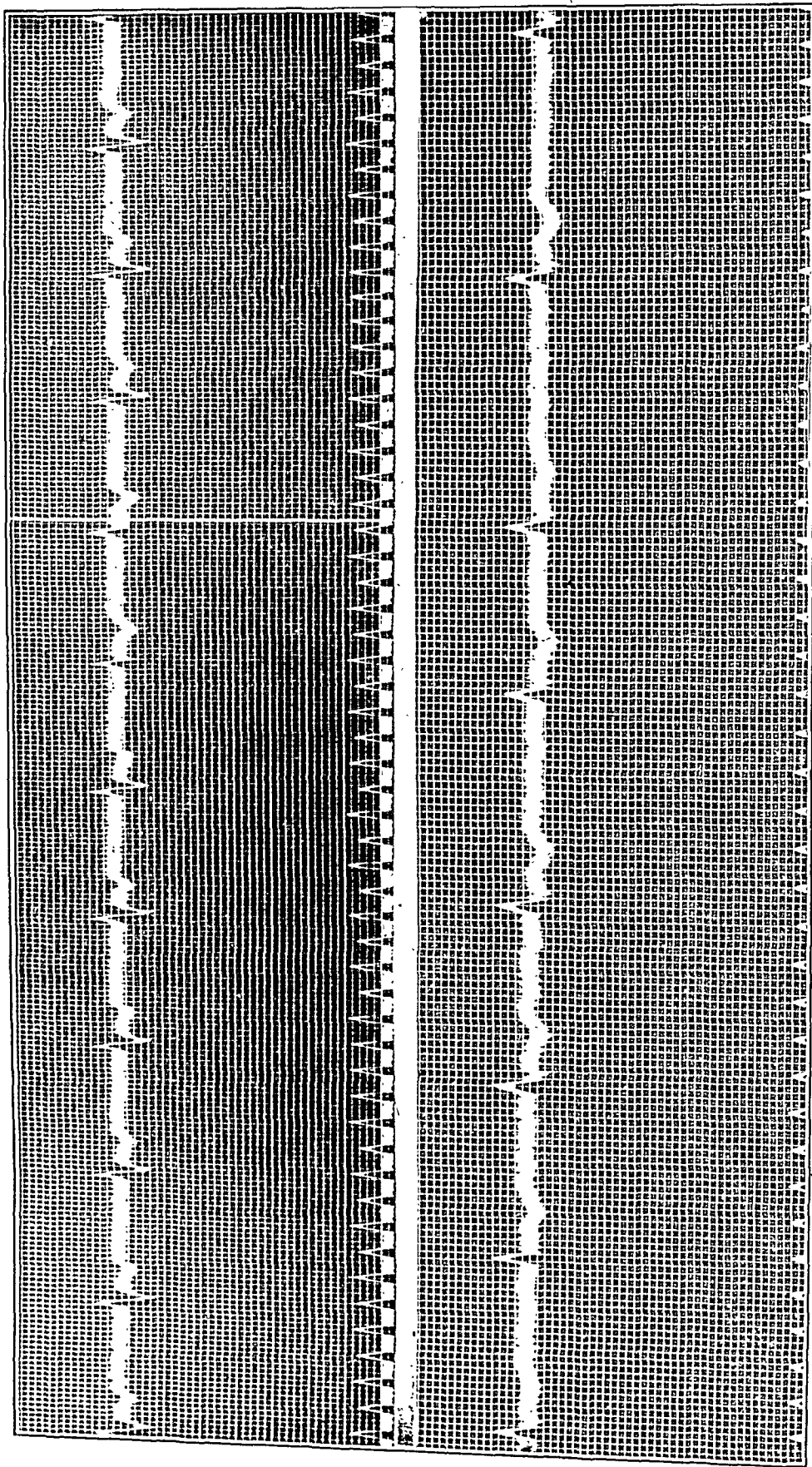
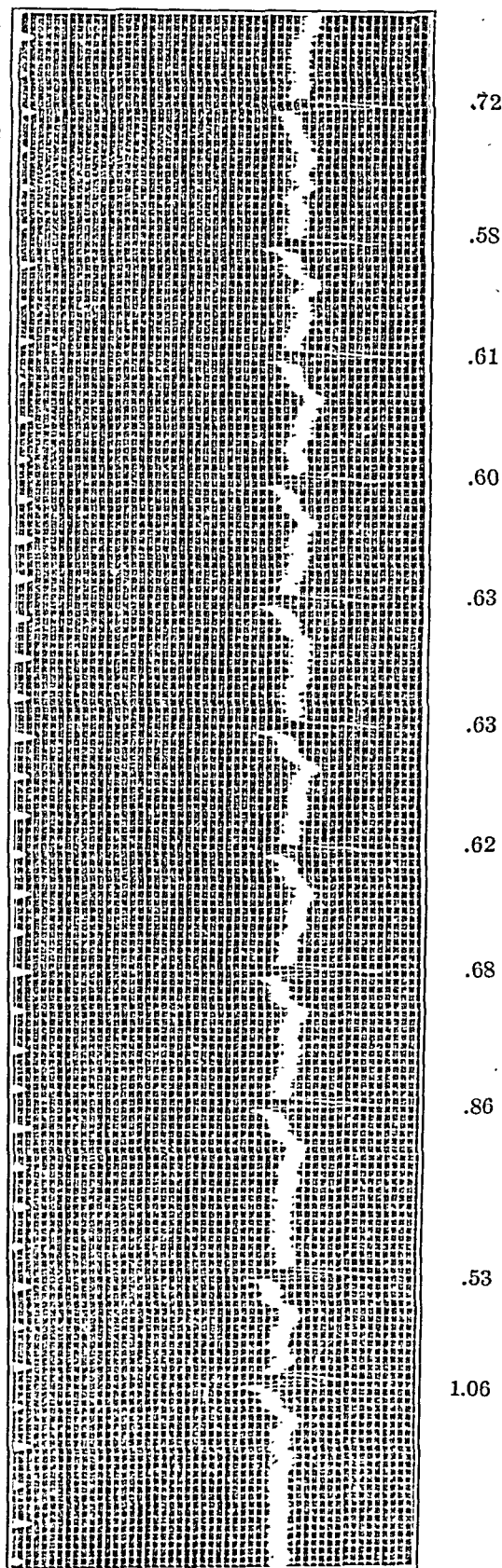


Fig. 1.—Case. 3. Upper tracing shows auricular fibrillation with a regular ventricular rate of 59.6 per minute. Lower tracing taken thirty-six hours later shows irregular ventricular rhythm rate 55.9.

Fig. 2.—Case 1. Tracing shows auricular fibrillation with irregular ventricular response. Note constant length of five cycles in the center. Numbers above indicate interventricular intervals.



In Cases I and III right and left vagal pressure caused no variation in the ventricular rate. In Case XII, holding the breath, right and left vagal and ocular pressure and the subcutaneous injection of 3 mg. of atropin had absolutely no effect on the rate of the ventricle. Even if we should succeed in later cases in thus changing the rate, the existence of partial block will not be demonstrated since, as Hewlett¹⁴ has indicated, the rhythm originating in the *A-V* node may be extremely susceptible to vagus influence. Until it can be shown that there is a direct relation between the rate of auricular impulses in fibrillation (*f* waves) and the ventricular rate, there is still lacking the proof of the view that such cases are instances of partial block. Measurements of our records for evidence of a simple ratio between the fibrillation rate and the ventricular response were wholly unsatisfactory. In 7 cases the *f* waves were too fine to be of any value, while in others, including Case XII, in which various sternal leads were taken, the *f* waves were so irregular that no comparisons could be made. Successive waves varied by 0.03 second, and groups of three successive waves varied by as much as 0.05 second.

In half of these cases (see table) the resumption of the irregular rhythm was associated with a decrease in the ventricular rate (Fig. 1), and if we reject the hypothesis of partial block we must assume that digitalis accelerated the rate of the dissociated ventricles. This is confirmed by the relatively more rapid ventricular rate in those cases of complete heart-block with normally beating auricles when under digitalis as compared with similar cases not treated with digitalis, as noted above.

One is struck by the fact that, in reverting to an irregular rhythm, these hearts often give tracings in which, mingled with beats of varied length, runs of beats of the same length predominate. Fig. 2 is a tracing taken of Case I while the ventricular rhythm was irregular and shows five perfectly regular beats in succession with shorter and longer beats coming before and after them. This same patient previously showed a perfectly regular ventricular rhythm for several days. It is difficult to explain the regular rhythm as due to an idioventricular mechanism and then maintain that the tracing shown in Fig. 2, which has so many regular beats, is due to the customary partial block that always accompanies auricular fibrillation. Is it not possible that in both instances we are dealing with a partial block which at one time is varying and at the others constant?

Conclusions. Regular ventricular rhythm with a rate over 55 per minute occurred under digitalis treatment as a transient phenomenon is about 2 per cent of 614 cases of auricular fibrillation. Attempts were made unsuccessfully in 3 cases to vary the ventricular rate by vagal stimulation or vagal inhibition (atropin). There is no proof that this mechanism is due to constant partial

block similar to that of regular ventricular rhythm in auricular flutter, although this remains a possibility. There seems to be definite evidence that digitalis in many cases accelerates the dissociated ventricle.

BIBLIOGRAPHY.

1. Lewis, Thomas: *Heart*, 1912, 3, 279.
2. Mackenzie, J.: *British Med. Jour.*, 1911, 2, 872.
3. Lewis, Thomas: *Mechanism of the Heart-beat*, Paul Hoeber, New York, 1920, p. 306.
4. Gerhardt, D.: *Zentralbl. f. Herzkrankh.*, 1910, 2, 339, 373.
5. Cohn, A. E., and Lewis, Thomas: *Heart*, 1912, 4, 15.
6. Falconer, A. W., and Dean, J.: *Heart*, 1912, 3, 247, and 4, 87.
7. Freund, H.: *Deutsch. Arch. f. klin. Med.*, 1912, 106, 1.
8. Edens, E., and Huber, J. E.: *Deutsch. Arch. f. klin. Med.*, 1916, 118, 476.
9. Kahn, R. H.: *Zentralbl. f. Herzkrankh.*, 1910, 4, 361.
10. Taussig, A. E.: *Arch. Int. Med.*, 1912, 11, 355.
11. Neuhof, S.: *AM. JOUR. MED. SCI.*, 1923, 165, 34.
12. Lewis, Thomas, Feil, H. S., and Stroud, W. D.: *Heart*, 1920, 7, 191.
13. Lewis, T., Drury, A. N., Bulger, H. A., and Iliescu, C. C.: *Heart*, 1920, 8, 83.
14. Hewlett, A. W.: *Heart*, 1923, 10, 9.

RIGHT DIAPHRAGMATIC HERNIA OF THE SHORT ESOPHAGUS TYPE.

BY SOLOMON FINEMAN, M.D.,

FELLOW IN MEDICINE, THE MAYO FOUNDATION,

AND

H. MILTON CONNER, M.D.,

SECTION ON MEDICINE, MAYO CLINIC, ROCHESTER, MINNESOTA.

At the Mayo Clinic the incidence of diaphragmatic hernia has been 1 in 23,000. We find in the literature reports of 5 cases of para-esophageal diaphragmatic hernia, in which the esophagus was also shortened congenitally. Our case is probably of the same type, and we report it because of the rarity of the condition and because we wish to call attention to the fact, hitherto not mentioned, that this type of hernia is irreducible surgically.

CASES REPORTED IN THE LITERATURE. Dietlen and Knierim's¹ patient was a woman, aged twenty-four years, who complained of pain in the right chest, occurring shortly after eating. A roentgenogram revealed a shadow in the right chest, which was interpreted as fluid, but aspiration failed to reveal the presence of fluid. On subsequent roentgenological studies a right diaphragmatic hernia of the stomach of the short esophagus type was found.

Bund's² case of diaphragmatic hernia occurred in a male child aged eight months. The diagnosis was established at necropsy. A tumor of the posterior portion of the mediastinal pleura was found extending into the cavity of the right chest. The tumor

proved to be a hernial sac, containing the entire fundus and two-thirds of the body of the stomach, which had herniated through the hiatus of the esophagus. The pyloric end of the stomach protruded through this hiatus and lay beneath the lower surface of the liver. The esophagus lay directly behind the trachea and descended as far as the bifurcation of the trachea, coursed slightly to the right, then suddenly turned to the right and entered the hernial sac from above (Fig. 1).

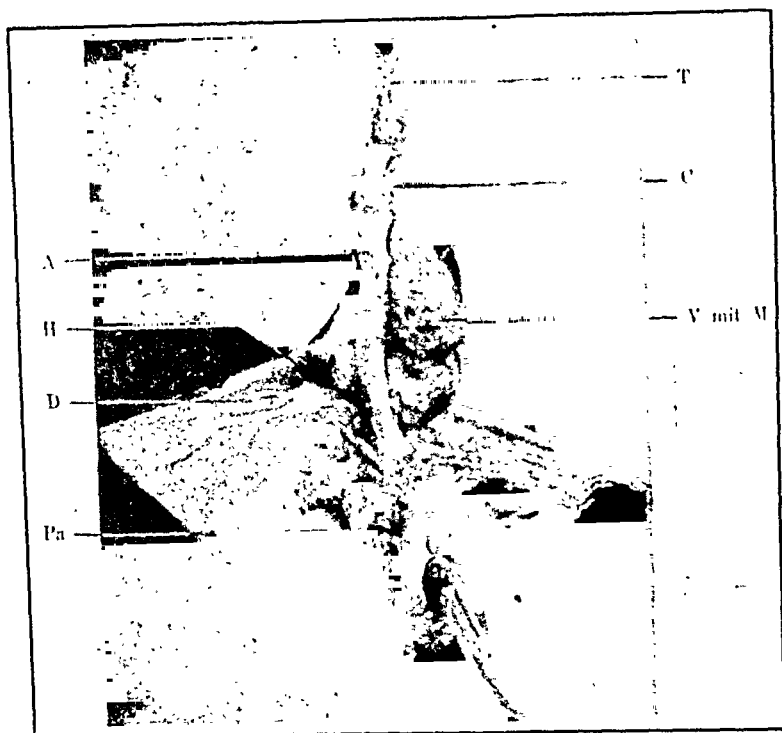


FIG. 1.—Bund's case. Note short length of esophagus at its entrance into the uppermost portion of stomach at C which lies practically entirely above the diaphragm D.

Plenck's³ patient was a man, aged forty-four years, who complained of a "delicate stomach," which had caused him considerable distress practically all his life. He had had several roentgenological examinations and a diagnosis of right diaphragmatic eventration had been made. He was finally operated on because of evidence of perforation and peritonitis; a right para-esophageal diaphragmatic hernia of the stomach was found. The duodenum was drawn vertically up against the esophageal foramen, and the contents of the stomach were seen exuding from the esophageal hiatus. All attempts at reduction proved futile. The author explains his failure to reduce the stomach on the basis of numerous adhesions and an inability to prolong the operation in view of the patient's critical condition. Death ensued in nine days. Necropsy revealed a shortened esophagus and abnormal position of the stomach, the major portion lying in the right chest. There was a

perforated gastric ulcer 3 cm. above the hernial ring. The esophageal hiatus formed the hernial aperture. The stomach was lying in the chest, with its greater curvature to the right and the lesser curvature to the left. The esophagus entered the stomach at the level of the ninth dorsal vertebra and measured 19.5 cm. from the cricoid cartilage. The average normal length of the esophagus is from 23 to 25 cm.

Huffman⁶ found the condition at the dissecting table. No data were obtainable except that the patient had died with symptoms indicating myocardial insufficiency. The greater portion of the stomach was in the posterior mediastinum, the pyloric end being in the esophageal hiatus. The esophagus ended 3 cm. above the esophageal hiatus.

In Tonndorf's⁷ case, observed at necropsy, the esophagus did not reach to the esophageal hiatus, and was 4 to 5 cm. shorter than the average. This man died at the age of seventy-six years.



FIG. 2.—Shadow at *a* above right diaphragm, mistaken at first for "encysted fluid" in chest.

REPORT OF A CASE OBSERVED AT THE MAYO CLINIC. **Case History.** (A380336.) J. H., aged twenty-two years, a painter, came to the Clinic because of marked pallor and palpitation. He had had these symptoms intermittently for many years, with periods of well-being between attacks. He had seen many physicians and had been treated for the past seven years for pernicious anemia. There was no history of gastric disturbance.

On physical examination the salient findings were marked anemia and a somewhat enlarged cardiac outline, over which systolic and diastolic murmurs were heard. A shadow above the right diaphragm was revealed by the roentgenogram (Fig. 2), which was interpreted as encysted fluid. We were unable to elicit physical signs to account for this shadow. The patient was admitted to hos-

pital and transfused. His general condition and anemia were improved considerably; the cardiac murmurs disappeared, but a roentgenograph again showed the previously noted shadow. Diaphragmatic hernia was suspected, and a roentgenological examination confirmed the

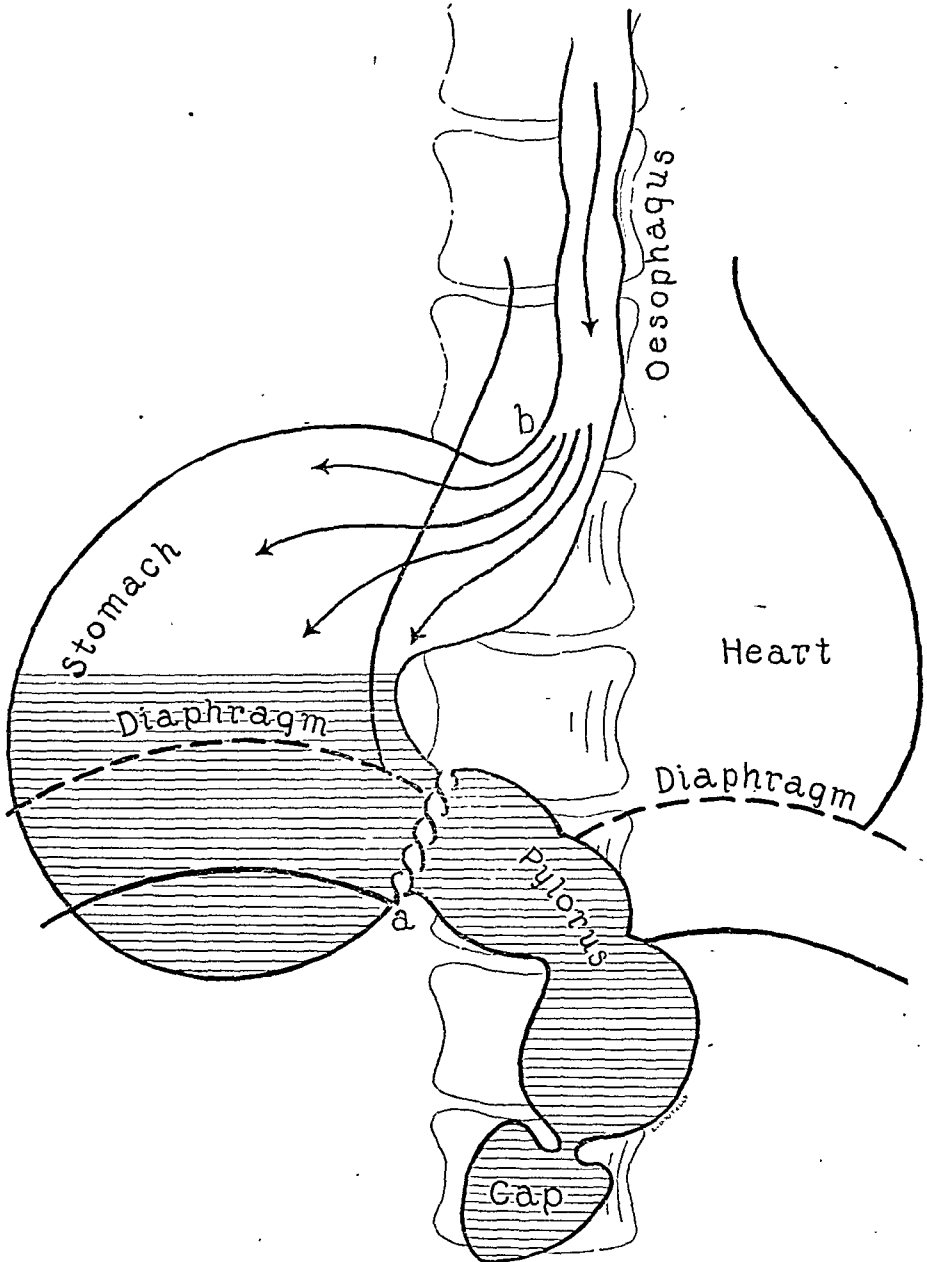


FIG. 3.—Diagram of esophagus, stomach and diaphragm. Note hernial opening in diaphragm at *a* and entrance of the shortened esophagus into the uppermost portion of the herniated stomach at *b*.

diagnosis. The esophagus was seen to descend on the left of the spinal column (Fig. 3), about three-quarters of the way down to the diaphragm. It then crossed the midline abruptly to the right and entered at a point well above the diaphragm into a pouch

lying in the right chest posteriorly. The passage of the bariumized meal failed to demonstrate any sharp kinking or blocking of the

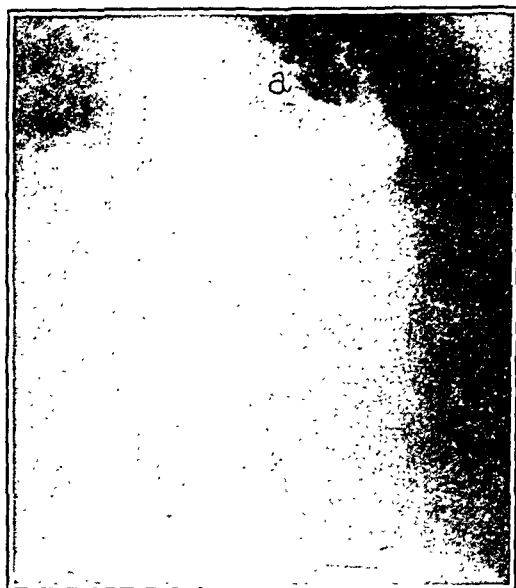


FIG. 4.—Postero-anterior roentgenogram taken in upright position showing herniated stomach in right chest. Note gastric rugæ at *a*. Compare with Fig. 1.

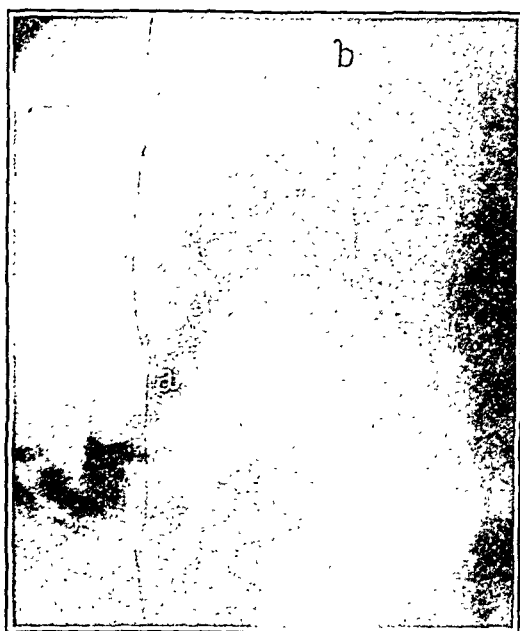


FIG. 5.—Anteroposterior roentgenogram, taken lying down, showing non-filling pressure defect in stomach at *a* caused by the diaphragmatic hernial ring. Note reversed position of greater and lesser curvatures, and absence of distortion or kinking of fundus and cardia at *b*.

esophagus. The barium mixture propelled by esophageal peristalsis emptied into the supradiaphragmatic portion of the stomach

in the form of an intermittent fan-shaped spray. The usual gastric bubble and gastric rugæ were visualized fluoroscopically

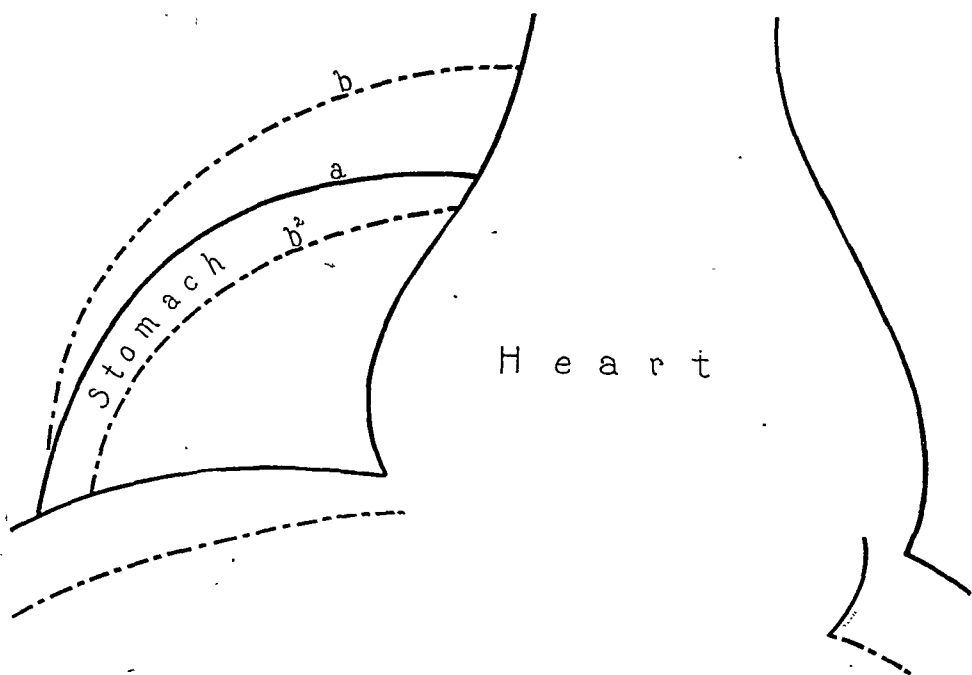


FIG. 6.—Fluoroscopic tracing of stomach at rest at *a*, and on full expiration, *b*, and inspiration, after administration of Seidlitz powder, *b²*.

and roentgenographically (Fig. 4). The opaque medium was then seen to pass through a diaphragmatic opening (Fig. 5) located posteriorly and practically in the midline into the pylorus which was lying below the diaphragm. The duodenum was normal. The

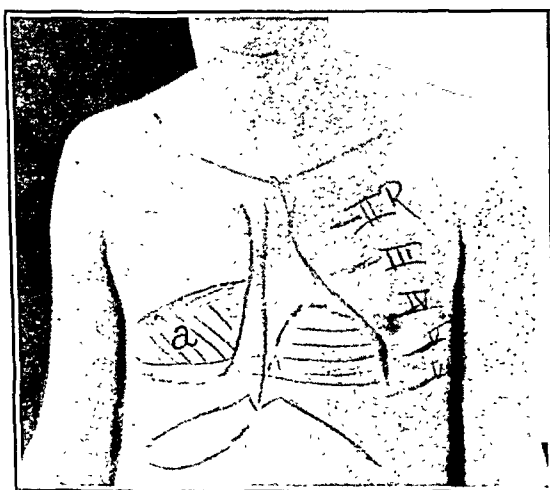


FIG. 7.—Percussion outline of tympanic area *a* corresponding to supradiaphragmatic portion of stomach after administration of Seidlitz powders.

diaphragmatic leaves moved normally, synchronously and freely. At a subsequent fluoroscopic examination the administration of

Seidlitz powder was seen to cause a moderate dilatation of the herniated portion of the stomach (Fig. 6). The outline of the gas-distended stomach could be percussed with some degree of accuracy (Fig. 7).

Using the kymographic method of Hardt and Joseph⁴ for the study of intragastric tension, it was determined that on inspiration and expiration the tension variations in the supradiaphragmatic stomach were the reverse of what is usually found in the normal stomach. With inspiration and expansion of the thoracic cage there was a fall in intragastric tension. With expiration and contraction of the thoracic cage there was a rise in intragastric tension. In this experiment no difficulty was experienced in passing a tube into the stomach. Free hydrochloric acid was demonstrated in the aspirated contents.

No operative procedures were attempted. This patient has been heard from recently, two years after his first examination, and he is not having symptoms referable to the hernia.

EMBRYOLOGY. Broman⁵ has shown that, in the human embryo, the lesser peritoneal cavity encircling the intestine is constricted by the fusion of the diaphragmatic anlagen, with the consequent formation of a blind sac, bounded on the left by the right mesodermal wall of the esophagus, on the right by the diaphragmatic anlage, and in part also by the right lung. In certain persons this bursa quickly disappears; in others, however, it enlarges and may often be found in the adult as a slit about 1 cm. or more in diameter, between the esophagus and right leaf of the diaphragm.

Bund² is of the opinion that a malunion of the diaphragmatic anlagen results in the persistence of a communicating canal between the lesser peritoneal cavity and the infracardiac bursa. In the presence of such a communication abdominal organs enter the infracardiac bursa and form a diaphragmatic hernia. He explains the shortening of the esophagus on the basis of a deficient fixation of its distal end to the esophageal hiatus, resulting from maldevelopment of the diaphragmatic segments which bound the esophageal opening. Plenck³ is of the opinion that the shortening of the esophagus can be explained either on the basis of a congenital hypoplasia, or by a lack of normal growth stimulant, due to the abnormal position of the stomach in the chest.

Discussion. On the basis of the roentgenologic findings, in part confirmed by the kymographic findings, we believe that we are justified in considering our case a congenital right para-esophageal hernia, of the short esophagus type. However, whether this particular case is or is not of this type, the fact remains that such hernias have been proved to exist, and that in 1 case an attempt at surgical reduction was made. In reviewing the literature on diaphragmatic hernia we find no mention of the fact that a com-

plete reduction of the stomach from the chest into the abdomen is impossible because of the congenitally shortened esophagus. It seems essential, for the sake of intelligent management, that every patient with diaphragmatic hernia of the stomach should have a careful roentgenologic examination with the specific object in mind of determining, so far as possible, the length of the esophagus.

Summary. The incidence of diaphragmatic hernia at the Mayo Clinic is 1 in 23,000 cases. The case of diaphragmatic hernia reported was on the right side, and in all probability of the short esophagus type. The intragastric tension in this case was found to be the reverse of what is usually found in a normal person. In such hernias, on account of the congenitally shortened esophagus, we believe complete reduction of the stomach from the chest into the abdominal cavity is impossible. Therefore, for the sake of rational management, every patient with diaphragmatic hernia involving the stomach should have a careful roentgenologic examination with the specific object in mind of determining, so far as possible, the length of the esophagus.

BIBLIOGRAPHY.

1. Dietlen, H., and Knierim, G.: *Hernia diaphragmatica dextra*, Berl. klin. Wehnschr., 1910, 1, 1174-1177.
2. Bund, R.: Ein Fall von rechtsseitiger Hernia diaphragmatica mit Austritt des Magens in den persistierenden Rezessus pneumatoentericus dexter, Frankfurter Ztschr. f. Path., 1918, 21, 243-257.
3. Plenck, A.: Zur Kazuistik der Zwerchfellhernien, Wien. klin. Wehnschr., 1922, 35, 339-341.
4. Hardt, L. L. J., and Joseph, E. G.: Kymographic Studies of Various Pathologic Conditions of the Stomach, Med. Clin. North America, 1923, 7, 63-79.
5. Broman, I.: Normale und abnorme Entwicklung des Menschen, Wiesbaden, J. F. Bergman, 1911, pp. 828.
6. Huffman, L. F.: A Case of Diaphragmatic Hernia Observed at Postmortem. Ann. Surg., 1920, 72, 665-667.
7. Tonndorf, W.: Wahre Zwerchfellhernien als Folge einer Wachstumshemmung der Speiseröhre, Deutsch. Ztschr. f. Chir., 1923, 179, 259-265.

THE HYPOPHYSEOBASAL AREA IN ITS RELATION TO THE PATHOGENESIS AND TREATMENT OF DIABETES INSIPIDUS AND POLYURIA.

(INCLUDING A STUDY OF THIRTY AUTOPSIES)

BY CHARLES E. DE M. SAJOUS, M.D., LL.D., Sc.D.

PROFESSOR OF APPLIED ENDOCRINOLOGY, UNIVERSITY OF PENNSYLVANIA GRADUATE
SCHOOL OF MEDICINE, PHILADELPHIA.

IN the issue of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES for November, 1922, I submitted that despite prolonged researches, the physiologists had been unable so far to point out the actual

function of any ductless gland and that this was due to the fact that the true role of these organs could only be discerned by a concomitant analytic and synthetic study of all branches of medical science bearing directly or indirectly upon the subject studied. Suggestive in this connection is a recent critical examination of the current views concerning the internal secretions by Prof. Swale Vincent¹ of the University of London, in which this physiologist emphasizes the need of a "reconsideration of our whole attitude in relation to the pituitary body." In keeping with this conclusion, it may be recalled that for over two decades, I have urged that the prevailing views concerning this organ were erroneous.

The particular labors to which Vincent refers are those of two French internists, Camus and Roussy (1913 and 1920),² and of Bailey and Bremer (1921).³ Camus and Roussy denied that polyuria was due to lesions of the hypophysis. They had observed intense polyuria after hypophysectomies in dogs, but careful necropsies showed that this occurred only when the basal tissues had been injured. When the hypophysis was removed alone without such injury, polyuria failed to appear; when, however, the basal tissues were injured and the hypophysis was left intact, polyuria occurred invariably. Their numerous experiments showed that the question of depth of injury in the basal tissues was of no moment; a superficial lesion sufficed provided it was located "at the level of the gray substance of the *tuber cinereum* in the vicinity of the infundibulum." Bailey and Bremer⁴ also found, in 13 adult dogs, that even an extremely minute lesion in the same area, *i. e.*, the parainfundibular region of the hypothalamus, invariably caused polyuria within two days, its duration depending upon the extent of the lesion and varying from six days to apparent permanence. It possessed all the characteristics of human diabetes insipidus. They found that an extensive lesion of the tuber cinereum was incompatible with life, the animals dying rapidly or after a period of apathy, in coma and convulsions. The integrity of the hypophysis was verified histologically in each case, thus eliminating this organ as a cause of the experimental polyuria induced.

Similar results were obtained by Houssay and Hug.⁵ They found that animals deprived of the hypophysis excrete the same amount of urine as the controls, and that where the animals drank water, the diuresis was actually less than in the controls. Houssay⁶ also denies that polyuria is due to hypersecretory activity of the hypophysis. His experiments showed that it was produced by lesions of the cerebral basal zone similar to that first defined by Camus and Roussy in 1913. He is inclined to believe, however, that the posterior lobe may structurally participate in the pathogenic process.

Indeed, to eliminate the posterior lobe from the pathogenesis of diabetes insipidus or polyuria introduces many difficulties. As shown by Falta, Marañon and others, compression of the median

and posterior lobes by an enlarged anterior lobe will also produce diabetes insipidus. Quite in keeping with this clinical and experimental fact is the polyuria of pregnancy in which, as is well known, the anterior lobe is enlarged and must, therefore, compress the posterior. But there is no involvement of the basal tissues here. As shown by Cyon, Masay and others, the slightest touch upon the exposed pituitary will produce a marked rise of blood-pressure while slight electrical stimulation will do likewise. Cushing⁷ observed also that mere manipulation of the posterior lobe sufficed to cause diuresis in experimental animals and sometimes intense and prolonged polyuria. Yet, while compression may cause it, Cushing likewise found that the opposite, sellar decompression by surgical measures addressed to the anterior lobe thus preventing pressure from the posterior lobe, brought on a severe polyuria—a result also noted in one of my cases. Again, if this identical lobe be disconnected from the basal tissues either experimentally as observed by Cushing and others, or accidentally as in the case of a boy shot in the head observed by Marañon and Rosique,⁸ prolonged polyuria is also produced.

Nor can we attribute any of these phenomena to a hypophyseal secretion. Not only can they all be produced, we have seen, by lesions above the hypophysis, and far away from it as we shall see, but injections of fluid from the cerebrospinal canal thought by Cushing and Goetsch to contain the specific hypophyseal secretion proved inert in polyuria, as shown by Houssay and Roman,⁹ Marañon,¹⁰ and Dixon and Cow,¹¹ where pituitary preparations proved active. An extract of choroid plexus, also thought by Weed and Cushing to secrete a pressor substance into the fourth ventricle fluid, was likewise tried by Dixon and Cow in polyuria but found inert, while hypophyseal extract at once produced its typical effects. In a comprehensive investigation of the subject, Jacobson¹² found "no definite evidence of the presence of a pressor substance in the cerebrospinal fluid suggestive of any posterior lobe secretion." Indeed, the bulk of present day evidence clearly indicates that, as stated by Souques, Alajouanine and Lermoyez¹³ at the recent Third International Congress of Neurology, posterior lobe preparations do not represent a secretion of this organ but only pharmacological products.

This is the view that I have urged many years, the effects of these products being at the time attributed mainly to adrenin, as first pointed out by Howell. The tissues of the posterior lobe not only give the chromophile test and other adrenalin color tests, as observed by Watanabe and Crawford,¹⁴ but they also raise the temperature, according to Rogers,¹⁵ and likewise the basal metabolic rate as recorded by McKinlay¹⁶—all phenomena which injections of adrenalin likewise provoke. Clinical experience has also shown that the effects of posterior lobe preparations are similar to those of adrenal

preparations, though more prolonged, owing to the presence of constituents resembling those of the cerebral cortex.*

The Hypophyseorenal Path. The pathogenesis of diabetes insipidus and polyuria no longer stands in the present inexplicable position, however, when, as its embryological origin indicates, the posterior lobe is regarded as a neural structure, and, as I first urged in 1908,¹⁸ *as the starting point of several sympathetic paths one of which extends via the tuber cinereum, the bulb, cord and splanchnic nerves and renal plexus to the vessels of the kidneys.*†

It is important to bear in mind in this connection, that there exists at the base of the brain a nuclear aggregate which can carry on all vegetative or somatic functions quite independently of the cerebral hemispheres proper. Its efficiency as such was amply demonstrated by Wilbur's frog, which lived five years after removal of its cerebral hemispheres, Goltz's dog, which lived eighteen months after the same procedure, including destruction of the optic thalami, and which even refused food made bitter with quinine, and Vulpian's demonstration that removal of the hemispheres, optic thalami, striated bodies, corpora quadrigemina and the cerebellum did not prevent the animals from crying out when an exposed nerve of its foot was pinched. Nor does removal of the both hemispheres from a pigeon prevent it from shaking off a fly that happens to alight on its head. So conservative a physiologist as Sir Michael Foster¹⁹ referring to such animals, wrote that "they may be kept alive and in good health for a long time" and that they exhibit "a spontaneity obviously betokening the possession, not merely of a conscious volition, but a certain amount of intelligence."

From my viewpoint, however, sustained by much accumulated evidence, the posterior or neural lobe of the pituitary, in keeping with its identity as an extension downward of the neural ectoderm which eventually becomes the floor of the third ventricle, forms part of the basal aggregate of nuclei to which Foster refers. I regard it in fact as forming *an individual mechanism similar to one of the cerebral motor areas, which I would term the hypophyseobasal area.*" Indeed, a careful analysis of this lobe by MacArthur²⁰ showed that "the chemical composition of the hypophysis resembled the gray matter or young nervous tissue in most respects" . . . "In

* This conclusion is not modified by the recent observation of Dixon,¹⁷ that pituitary extract injected into the cerebrospinal fluid or into the circulation caused the pituitary to secrete. That a balance was struck between the amount in the blood and the cerebrospinal fluid indicates mere diffusion, while the fact that the latter fluid gave the chemical and physiological reaction of pituitrin is but a normal outcome when the posterior pituitary is considered as a nervous structure, since both fluids would contain the same neural constituents. From my viewpoint the actual participation of a pituitary "secretion" in the process is only assumed.

† The term "path" employed here is intended merely to denote a nervous connection between the hypophyseobasal area and the kidney, the true identity of which is still to be determined. There are a number of descending tracts concerning which our anatomical knowledge is still obscure.

those respects in which the two lobes differ the posterior is more like the gray matter than the anterior," a fact which various his-

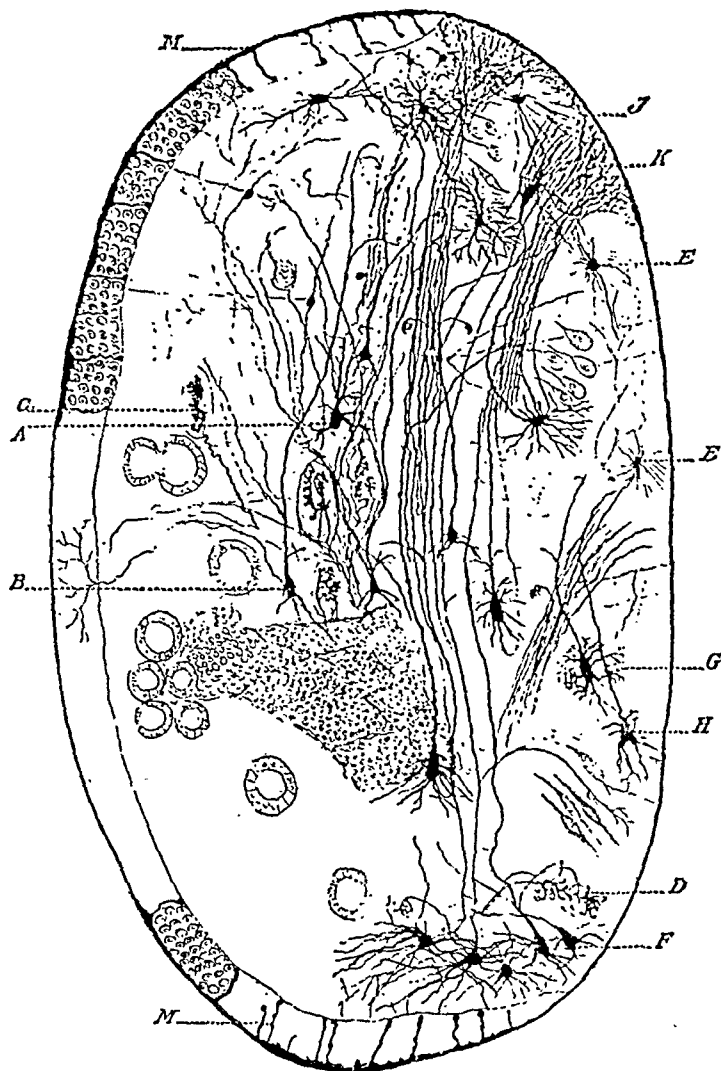


FIG. 1.—Vertical section of the neural lobe of the hypophysis. (Berkley.) Schematic, to illustrate the various types of cells in the 2000 sections of this lobe examined. *M*, outer layer over posterior surface of lobe, composed of gray matter (Luschka, Müller), and ball-tipped ependymal cells; *A*, widely distributed cells with many ramifications; *B*, similar cells, centrally located with long upward, brush-tipped processes; *C*, centrally located cells, resembling closed follicles, with comb-like tufts; *D*, neuroglia cells; *E*, spider cells in large quantities similar to, but larger than, those in cerebral tissues; *F*, ganglion cells which traverse entire organ upward and end in infundibular area; *G*, large pyramidal cells; *H*, pyramidal cells with short dendrites; *J* and *K*, ramifications of long dendrites, tufted figures and feathery protoplasmic cells, also cells covered with thorns which give off strong dendrites. These cells are not found elsewhere in the nervous system and occur in the upper border of the neural lobe "along the space formerly occupied by the infundibular duct."

tologists had also observed. Luschka,²¹ Müller²² and others who studied the hypophysis from myxine to man found that its gray matter extended upward along the infundibulum up to and including

the floor of the third ventricle. So marked were these histological characteristics, coupled with many facts, biological, physiological and clinical, recorded and personal histological studies, that I ventured in 1907 to term the hypophysis—including the basal nuclei—the *somatic brain* to convey its physical limitation to body or vegetative functions, as distinguished from the *psychic brain*, the organ of mind, the pallium or cerebral hemispheres overlying it.

There can be no doubt regarding the identity of the posterior lobe of the hypophysis as a nervous organ. In keeping with embryological and morphological data which have caused it to be termed by anatomists the "neural lobe," Berkley²³ found histologically that it contained numerous typical nerve cells. Osborne and Vincent²⁴ and other observers have likewise described true nerve cells and fibers in the posterior lobe. Moreover, knowledge gained in recent years on the histochemistry of the lipoids has shown that the glia cells claimed to be alone present by the opponents of this view, are composed of phospholipoids and cholesterin similar to those found in the myelin of the nerves at large and the brain. In the illustration of the posterior lobe submitted herewith, one of Berkley's plates, this organ is shown to contain a close and thick plexus of fine fibers which ramify among the nerve cells, constituting "terminal arborizations of a bundle which passes downward in the infundibulum," while other fibers pass upward to the basal tuber cinereum.*

As to the relations of the hypophysis with the basal tissues by nerve paths, Cajal found that the fibers passed up mainly to the giant-celled nucleus in the basal tuber cinereum immediately above the infundibulum. This nucleus, the largest of a series of paired ganglia, was described by both Lenhossek and Kölliker, and termed by the latter histologist, *nuclei tuberii*, owing to their situation in the *tuber cinereum*. This region in turn was described by Sir Michael Foster as "*a continuation of the spinal gray matter.*"

Authors who refer to the infundibulum as a canal through which a secretion is supposed to pass up to the third ventricle, overlook the fact recalled by Piersol²⁵ that, while "in the very young child the infundibulum retains to some extent its original character as a hollow outgrowth from the ventricle, in the mature subject this cavity, the recessus infundibuli, has mostly disappeared and the stalk is solid save for a slight diverticulum within its upper and widest path," thus affording a path for the nerve fibers to the basal tissues. As shown in the illustration herewith (*J* in the descriptive text) long dendrites are present "in the space formerly occupied by the infundibular duct."

* The remarkable activity of hypophysis sicca and pituitrin, both posterior lobe preparations, bespeaks the presence in this lobe of a rich supply of nuclear materials besides adrenin. This in itself stamps as misleading the often-published statement that the neural lobe contains but a few neuroglia cells and degenerated nervous tissue, that it is but a vestigial organ, and so forth.

That the hypophysis influences the body at large, including the brain, has been noted by various physiologists. De Cyon²⁶ and also Masay²⁷ found, we have seen, that the slightest touch of the organ through an opening in the sella turcica, and only after the animals had entirely recovered from the operation, produced a marked rise of blood-pressure and reduced the heart beats. Pirrone²⁸ thought he disproved these observations because he found that stimulation of the basal tissues above the hypophysis produced the same effects as those observed by de Cyon and Masay. But he only confirmed their views as to the peripheral effects described, and also my own (1903)²⁹ that it is through nerve paths *beginning* in the hypophysis and passing through the tuber cinereum via its nuclei that these vasomotor effects were evoked. Weed, Cushing and Jacobson³⁰ also found that faradization of the pituitary gave rise to glycosuria, a fact clearly explained by the effect of impulses through a path from the same organ to the adrenals which I have described elsewhere.³¹ Finally, I might also recall the observation of Schäfer³² that experimental injury of the hypophysis gave rise to polyuria, a result due to impairment of the hypophyseorenal nerve-path previously referred to as having been first described by myself in 1908¹⁸ and the existence of which will now be further sustained.

Diabetes Insipidus Due to Lesions along the Hypophyseorenal Path. The need of such a path to explain the pathogenesis of diabetes insipidus was shown by a personal study of thirty and odd unselected cases reported in the literature of the lasty thirty-eight years. These necropsies clearly show by lesions situated all along the hypophysiorenal path extending from the hypophysis *per se* to the kidneys, that this one disease—or symptom of many local pathological processes—diabetes insipidus, can be produced by impairing the functions of this path *anywhere throughout its course*.

Lesions of the Posterior Lobe per se. Twelve of the recorded cases showed that the neural lobe alone could be the seat of various kinds of local processes capable of causing diabetes insipidus. Benario³³ described a case in which a gumma was found in this lobe at autopsy. Two similar observations have been recorded by Sequeira³⁴ and Berge and Schulmann,³⁵ Marañón³⁶ also refers to cases reported by Spanhock and Goldzeiher. Metastatic cancer of the posterior lobe was found by Simmonds³⁷ in 3 cases with intractable polyuria. In 1 similar case recorded by Neuburger,³⁸ and in 2 reported by Sekiguchi,³⁹ all 3 showed marked polyuria; [the basal gray matter was also examined and found to be the seat of no pathological changes.

Lesions in Both Lobes or in the Infundibulum. Six of this class were recorded. In a case of diabetes insipidus autopsied by von Meyenburg,⁴⁰ a cancerous process included both the middle and posterior lobes. Cushing observed a case in which metastatic lymphosarcoma of the infundibulum was found postmortem. In a

case of teratoid cyst recorded by Globus and Strauss,⁴¹ both lobes and the infundibulum were compressed. In one reported by Newmark,⁴² the posterior lobe and nearly all the pars intermedia were also found destroyed. Luzzatto⁴³ observed a case of polyuria in which autopsy showed that destructive hemorrhage of the posterior lobe had separated the latter from the infundibulum. In another reported by Chauffard,⁴⁴ a fungous tumor had destroyed the hypophysis without involving the basal tissues.

Lesions of the Infundibulum and Tuber Cinereum. Two cases had been recorded in which the diabetes insipidus was due to lesions involving the nerve path in these areas. In one reported by Römer⁴⁵ the disease proved at autopsy to have been due to a tumor involving both the posterior lobe and the overlying basal tissues; in one observed by Lhermitte,⁴⁶ a syphilitic lesion was found to involve both the infundibulum and the tuber cinereum. That puncture of the latter produces polyuria is recalled by Veil.⁴⁷ Also emphasizing this fact, Leschke⁴⁸ states that bullet wounds, tumors, gummata, tubercles and other lesions in this location may all produce this condition, without lesion in the hypophysis proper, in accord with the observations previously submitted.

Lesions in the Bulb. Seven cases of this class examined post-mortem were found. Lecorché and Talamon⁴⁹ over thirty years ago urged the importance of syphilitic sclerogummatous lesions in the neighborhood of the floor of the fourth ventricle as a cause of diabetes insipidus and reports 2 cases in which nervous phenomena due to irritation of local nerve paths occurred. Ebstein,⁵⁰ in 6 cases of diabetes insipidus due to syphilis, found lesions in the medulla oblongata in 3. Marinesco⁵¹ reported a case in which the autopsy showed a gliosarcoma in the floor of the fourth ventricle. Even edema in this region as observed by Weiszbarth⁵² may cause diabetes insipidus. I might recall in this connection that as shown by Bernard, a *piqûre* very near to that which causes glycosuria will cause polyuria; also that *piqûre* of the tuber cinereum produces the latter; and, finally, that diabetes mellitus and diabetes insipidus often occur together.

Lesions of the Spinal Cord and Splanchnic Nerves. That diseases of the spinal cord—which in the present connection would involve the hypophyseorenal path—sometimes show diabetes insipidus as a complication is well known. Fitcher⁵³ refers to a case of tabes seen by Schlesinger; to one of spastic paralysis reported by Westphal; to one of diffuse tumor of the cord observed by Shultze; to some of syringomyelia seen by Krause, and of hereditary ataxia reported by Friedreich in which polyuria was more or less persistent. As to the paths from the cord, "cases of diabetes insipidus are also recorded," writes Eichhorn,⁵⁴ "in which degenerative changes have been found in the sympathetic system, notably in the coeliac plexus and the great splanchnic nerves." These, as is well known, form,

with renal branches of the lesser splanchnic, the renal plexus which supplies nerves to the renal arteries.

A connection with the hypophysis has also been urged recently (1916) by Motzfeldt,⁵⁵ of Christiania, who, after a critical study concluded that "although the disease is comparatively rare, a number of cases had been recorded during recent years" (to which the autopsied cases I have quoted above may be added) in which "their connection with the hypophysis has been proved beyond a doubt" . . . "The posterior lobe of the hypophysis seems to exert a constant physiological influence on renal functions."

How are the kidneys influenced by the hypophyseorenal path through the splanchnic by stimulation and diuretics? I may recall in this connection that in 1908¹⁸ I submitted that "when the flow of urine is to be increased, the renal arterioles are dilated by vasodilator terminals of the sympathetic which reach the organ by way of the splanchnic nerves and the semilunar ganglia. The glomerular tufts being thus traversed by a greater volume of blood, the components of urine are thus filtered out into Bowman's capsule." That increased cellular activity, through vasodilation with congestion, as first taught by Bernard, is one of the main features of active diuresis and of diabetes insipidus is emphasized by its pathology. "The only thing that can positively be stated," says Fletcher⁵⁶ in reference to this disease, "is that it is due to some nervous influence causing a vasomotor disturbance of the renal vessels, leading to persistent congestion of the kidneys. The only constant finding at autopsy is enlargement and congestion of the kidneys."

On the whole, the foregoing data tend to show that diabetes insipidus can be produced when any condition, gumma, tuberculoma, cancer, focal hemorrhage, cicatricial tissue, etc., located in or involving either the posterior lobe, the infundibulum, the overlying tuber cinereum, or any of these structures jointly, or any other portion of the hypophyseorenal path, sufficiently interferes with the transmission of its impulses to the renal vascular system to allow too great a volume of arterial blood to traverse the organ and its secretory elements.

Besides causative lesions in the hypophyseorenal nerve-path, however, there are various disorders which induce diabetes insipidus or intense polyuria by acting upon this path in other ways.

Diabetes Insipidus and Polyuria Due to Compression of the Hypophysis and its Basal Nerve Paths. Pregnancy is a familiar cause of diabetes insipidus. Though a physiological process, it is well known that the anterior lobe becomes enlarged. In the light of the foregoing facts this is due to the pressure exerted upon the nervous elements of the posterior lobe, the osseous posterior wall of the sella affording the necessary resistance, which pressure interferes with the functions of the organ's nuclei, and inhibits the formation of the

impulses to the kidneys. All this applies also to acromegaly, which often includes diabetes insipidus in its symptom-complex. The polyuria may be either temporary, as is often the case in pregnancy, or if microscopical lesions develop in the hypophysis as a result of the pressure, it may last indefinitely. Hypophyseal tumors are also known to cause diabetes insipidus. We thus have a series of factors capable of evoking this symptom and which if located in the anterior lobe can compress posteriorly the pars intermedia and the posterior lobe and thus inhibit more or less the functions of the latter. It would be difficult to prove that the basal tissues are invariably involved in the pathogenic process of such cases otherwise than as a conducting path.

Ample evidence also attests, however, the causative influence of pressure from disorders in structures external to the hypophyseobasal area. In a case observed by Lépine,⁵⁷ for instance, the autopsy showed a tumor of the optic thalamus, immediately above, therefore, the tuber cinereum. The polyuria had appeared suddenly and the large size of the tumor indicated that it compressed the latter and probably, as Lépine thought, "the pedicle of the hypophysis."

In this case pressure must clearly have blocked the passage of impulses to the kidneys. A very similar case was recently reported by Ricaldini⁵⁸ in which infantilism of the hypophyseal type was present together with diabetes insipidus. At autopsy a sarcoma was found between the optic thalamus and the tuber cinereum. The latter itself, the infundibulum, and the hypophysis were found macroscopically normal; microscopically, however, slight hemorrhagic foci and lymphocytic invasion of the posterior lobe, the head, in other words, of the hypophyseorenal path. Suggestive in this connection is the remark of Beck⁵⁹ in reference to dystrophia adiposogenitalis, that "when associated with tumors in the neighborhood of the hypophysis, especially those involving the chiasm and subthalamic region or with basilar syphilitic meningitis, a true diabetes insipidus may develop." Even fluid compression may cause it. The aqueduct of Sylvius being very small, inflammatory or neoplastic disorders in its neighborhood may readily close it and cause sufficient retention of cerebrospinal fluid in the third ventricle to produce marked pressure upon the nuclei and nerve paths in the tuber cinereum. The pressure may even be exerted from below the hypophysis, as in a case reported by Hamilton⁶⁰ in which the cause of the diabetes was found at postmortem to be a tumor of the circle of Willis.

The polyuria of encephalitis lethargica is probably due to a similar process. Such cases have been reported by Briand and Rouquier,⁶¹ Gosset and Gutmann⁶² and Bénard.⁶³ The neural lobe of the hypophysis was first associated with normal sleep by myself (1903),⁶⁴ then by Salmon (1905)⁶⁵ and others. Bénard, by administering injections of fluid extract of pituitary reduced the polyuria markedly.

so to say at will, the effect lasting only as long as the remedy was used, about twelve hours. A single injection only caused a reduction of the polyuria in twenty-four hours from 19 liters to 5.8 liters. Bénard attributes the intense polyuria to involvement of the hypophysis and the overlying tissues. Pressure by the cerebrospinal fluid in the third ventricle upon the tuber cinereum not only affords a foundation for this interpretation, but the familiar beneficial effects of lumbar puncture in all forms of meningitis is supplemented in the present instance by the fact, first shown by Herrick and confirmed by Cammidge,⁶⁶ Tucker⁶⁷ and others, that lumbar puncture may also prove beneficial and even curative in diabetes insipidus.

Epidemic encephalitis was attended by diabetes insipidus in a case recently reported by Hall.⁶⁸ Some lesion other than the epidemic encephalitis caused pressure upon the tuber cinereum, for there were ocular symptoms, unilateral facial paresis, while the patient was a mental defective. The presence of such a lesion, probably a tumor below and behind the optic thalamus (the sella turcica then showing no roentgen-ray change, as specified) was indeed shown by the return of the patient two years later with marked diabetes insipidus. But neither adrenalin or pituitrin appeared to reduce the urine output, although the latter preparation caused a rise of blood-pressure and relieved the extreme thirst. The renal vascular paresis was so complete in this case that the vasoconstrictor action of the pituitrin could not manifest itself in the kidneys though active throughout the body at large.

Compression from lesions within the hypophysis, or of external origin, upon this organ, the basal tissues or the nerve paths it contains, may thus provoke diabetes insipidus. While the two structures appear capable of causing this symptom separately, the fact remains that a neural path beginning in the hypophysis and passing through the basal tissues seems alone capable of explaining its production. An effort to do so by means of one or more "secretions" soon proves fruitless.

Diabetes Insipidus and Polyuria Due to External Traumatism; Emotional Stress, Etc. Falls upon the head, concussions, basal skull fractures, fright, etc., have long been accepted as causes of diabetes insipidus and also of various pituitary disorders, notably acromegaly, hypopituitarism and the adiposogenital syndrome. Numerous cases of diabetes insipidus are also clearly due to violent emotions. Marañon⁶⁹ observed five such patients and refers to instances recorded by Lereboullet, Van der Heijden, and Germani.

The similarity of the posterior or neural lobe of the hypophysis to the cerebral cortex observed by histologists previously referred to, and many other facts which led me many years ago to refer to this lobe, including its nervous connections with the anterior lobe and the overlying basal ganglia in the tuber cinereum, as a somatic brain, also caused me to refer to it as a *sensorium commune* (1903)⁷⁰

upon which fright, shock, anger, etc., could react by jarring its cellular elements. I may recall in this connection the independence of this organ from the overlying psychic brain as illustrated by the decerebrated animals, frog, fowl, dog, etc., previously referred to. Such an animal, in fact, as emphasized by Sir Michael Foster, "is not wanting in what we ordinarily call a 'will.'" Nor would any one deny its manifestations, besides instinctive acts in lower forms devoid of skull or brain, the amphioxus for example, to which low form Andriezen traced the structures which ultimately become the pituitary body.

All this refers as well to sensibility. Any one who has worked with amphioxus, for instance, knows its almost lightning-like response to any external excitement, the gentlest stimulus or fright, despite the absence in this animal of cerebral hemispheres. Even in man, what sensibility the cerebral cortex affords is limited to "tactile discrimination and localization and perhaps of the finer shades of temperature" and that only in the postcentral convolution. Brubaker (1922),⁷¹ who gives these limitations also, refers to Charles K. Mills as stating that "innumerable cases have been reported of lesions of the motor area (the precentral convolution) without the slightest impairment of sensibility;" these included excision of portions of the motor cortex. As to where a cutaneous injury actually reacts, Schäfer⁷² referring to decerebrated animals, concludes: "This no doubt lands us in the unsatisfactory position that we are certainly unable to say in what part we are to localize cutaneous sensibility, or even if it is localized at all in the cortex."

The spinal cord at once suggests itself as a factor in any morbid process due to exogenous trauma, but even here we are brought back to the hypophyseobasal area, *i. e.*, the *sensorium commune*, for as Foster states in this connection, "the phenomena presented by animals deprived of their cerebral hemispheres show that this machinery of coördination is supplied by cerebral structures lying *between the cerebral hemispheres above and the top of the spinal cord below.*"* Referring to this area as the "tegmental region from the bulb upward," he also states that this region through which ascends the fillet is "a probable path of sensations of one kind or another from the body at large."

That this same area and the hypophysis itself are directly concerned with the perception of common sensibility is shown by the frequency with which pain in one region or another is recorded by many investigators in acromegaly. This pain may be localized in the soft tissues of the face and regarded as "neuralgia" or extend over the entire body. Pirie noted shooting pains in combination with paresthesia, tingling and numbness, and he refers to Sternberg as remarking "particularly on the occurrence of pain and paresthesia

* The italics are my own.

as valuable signs for diagnosis in the *early* stages of the disease." In his own pitiful case, Mark⁷³ distinguishes emphatically what he terms his "faceache" from the characteristic headache of the disease; it was persistent and always occurred on the left side. Cold air greatly aggravated the intensity of this "neuralgia" or "migraine." Suggestive in this connection is the fact that de Cyon⁷⁴ found experimentally in a large number of animals that removal of the hypophysis annulled the nasal sensory reflexes, sneezing, etc., but also that all the nerves including the fifth glossopharyngeus "lost their reflex influence." I have submitted considerable evidence elsewhere⁷⁵ showing that touch, hearing and taste were also connected with the hypophysis. We have seen that Goltz's decerebrated dog refused food which contained quinine, that a decerebrated pigeon will shake off a fly alighting upon its head, etc.;—all attesting to the presence of a *sensorium commune* distinct from the brain itself, purely autonomic or vegetative in the normal organism.

As to the modes of production of the many peripheral symptoms observed in hypophyseal disorders, acromegaly in particular, paresthesias, pain, photophobia, hyperacousis, tinnitus, conjunctival congestion, catarrhal disorders of the respiratory tract and the Eustachian tubes, bulimia due to passive congestion of the gastric mucosa, congestive lethargy, heat flushes, edema, etc., they are similar to the cause of polyuria, *i. e.*, passive vasodilation in the tissues which are the seat of the symptom. In pain or hyperesthesia, for instance, the cutaneous arterioles are passively congested and their sensory nerve endings, irritated by the excess of blood they receive, convey pain or heat impulses back to the *sensorium commune*. This means that we must consider the hypophysis capable of receiving sensory and giving out motor impulses. We have seen that such is evidently the case, the inward impulses reaching this organ by way of the median fillet—a decussation from the funiculus gracilis—while the motor impulses are transmitted to the vessels by way of the spinal and sympathetic systems. All the organs and tissues dominated by this hypophyseobasal somatic brain, are functionally active in proportion as the volume of arterial blood which passes through them is great. Its highly differentiated cells preserve the equipoise of this blood supply and it is to variations of activity of the various cellular groups, which differ greatly as shown in the illustration on page 683 that the many different phenomena awakened by the organ are due.

An important fact to bear in mind in this connection is that diabetes insipidus is the maximum expression of exaggerated diuresis. Gradually descending the scale the severity of the symptom from marked polyuria down to copious diuresis, we reach the emotional causes witnessed during excitement, fear—as observed in troops when first led to attack. These are due to temporary relaxation

of the renal vascular channels under the influence of the emotional stress acting centrally upon the hypophyseal sensorium, commune.

Treatment. The treatment of diabetes insipidus was very unsatisfactory and uncertain in its results when Francesco Farini (1913)⁷⁶ gave us what constitutes virtually a specific by introducing the use of pituitary extract in hypophyseal polyuria. The posterior lobe fluid preparations given hypodermically in 10 to 15 minim (0.6 to 1 cc) doses, have been found to act very efficiently, not only reducing markedly the polyuria but also the intense thirst. In the light of the views submitted above, the explanation of this result suggests itself: The posterior lobe preparation acts upon the renal arterioles as it acts elsewhere in the body; it promotes their contraction. That this is the result of a pharmacological action was recently shown by Weir, Larson and Rowntree⁷⁷ who found that these preparations acted when all the nerves to the kidneys had been severed.

Unfortunately, the action of pituitary preparations is ephemeral and the injections must be administered daily at least to sustain the beneficial effects—two defects which render the method difficult except in hospitals. To obviate them, I used successfully in a very severe case of diabetes insipidus due to pituitary tumor in a child aged twelve years, and which persisted despite a decompression operation, a combination of the hypophysis sicca, $\frac{1}{10}$ gr. (0.006 gm.) and ergotin, 1 gr. (0.06 gm.) in a capsule. This was given orally three times daily, the ergotin being added to reinforce the vasoconstrictor action of the posterior pituitary. The polyuria gradually decreased until the daily output became normal. Up to the time of the present writing, two years after this treatment ceased, the polyuria had not returned. Rees and Olmstead⁷⁸ found in one case that by covering the posterior-pituitary preparation used with salol, the effects were as satisfactory as when the hypodermic method was used, provided, however, that in addition to the daily dose, one be administered also at bedtime.

The enuresis of children is also due in some instances to functional adynamia of the hypophyseobasal area. Hence the beneficial effects of posterior lobe preparations in the treatment of many of these cases.

The apparent innocuousness of removal of the posterior or neural lobe recorded by Paulesco, Cushing and others, would seem calculated to offset the deductions submitted. But it only proves anew that this lobe at least is not a secreting organ, since we know that removal of *bona fide* endocrine glands, the thyroid or adrenals, for example, gives rise to marked phenomena. Conversely, as a coördinating center, the neural lobe, from my viewpoint, contributes no hormone to the life process itself, but forms part of a sympathetic nuclear mechanism which regulates the admission of arterial blood to the cellular elements. When we administer preparations of this lobe, therefore, we add to the blood an agent rich in organic phos-

phorus and adrenin which, by reducing the caliber of its arterioles, restores the normal renal circulatory equilibrium and thus prevents the polyuria.

Again, removal of the *entire* hypophysis, we have seen, was found by Camus and Roussy and Houssay and Hug not to be followed by polyuria. Even though this does not apply to all experimental observations, Houssay, for instance, having observed a temporary polyuria after this procedure, the fact remains that removal of the anterior lobe as well as the posterior so modifies the whole functional and metabolic activities of the body that it hardly affords dependable results. In 6 dogs subjected to this radical operation by an expert operator, Blair Bell,⁷⁹ one died under anesthesia, but the remaining 5, even though they recovered and partook of food, died in from twenty-two to thirty-six hours. They became somnolent and "although it was sometimes possible to rouse them from this condition and to get them to stand and take food, they quickly became somnolent again as soon as they were left alone. After a few hours the respirations became very slow and coma set in; finally death supervened." If it is now recalled that I³¹ have also traced a path from the hypophyseobasal area to the adrenals and that ample evidence⁸⁰ has confirmed the personal view of 1903 that the adrenals sustained tissue oxidation, the cause of death from respiratory failure by removal of the whole hypophysis becomes plain. Yet, the survivals of hypophysectomized animals recorded by Camus and Roussy, Sweet and Allen⁸¹ and others, find a normal explanation in the fact that removal of the hypophysis leaves all the basal tissues intact as well as the bulbar vasomotor and other coördinating centers to carry on approximately (as shown by obesity or other disorders observed in operated animals) the vital processes with which the hypophyseobasal area is concerned. The vasomotor center is also a potent compensative factor in all conditions external to it that affect the circulation and produce CO₂ toxemia; it probably aided, when stimulated by the carbon dioxide, in arresting the polyuria observed in Houssay and Hug's hypophysectomized dogs, by favoring contraction of the renal arteries.

Conclusions. Swale Vincent's conclusion that the prevailing attitude concerning the functions of the hypophysis should be reconsidered in view of the labors of Camus and Roussy, Bailey and Remer, Houssay and others being fully justified, the line of research reviewed in the foregoing pages is intended to point out:

1. That it is because the functions attributed to the posterior lobe of the hypophysis by physiologists and others have been erroneous from the start that Swale Vincent's conclusion that the attitude in relation to this organ should be reconsidered now imposes itself.

2. That the investigations of Camus and Roussy and others named do not demonstrate that the posterior lobe of the hypophysis

takes no part in the pathogenesis of diabetes insipidus or polyuria; they only show that lesions of the tuber cinereum can provoke these disorders, and that the latter can be produced without the participation or need of a secretion from the hypophysis.

3. That the effects of lesions upon, the slightest contact with, or manipulation of, the posterior lobe; its embryological origin as a neural organ; its histological and chemical similarity to the cerebral cortex; the various disorders which may be strictly localized in it; its autonomous role with the overlying tuber cinereum as shown by decerebrated animals, and other facts submitted, point to this *hypophyseobasal area*, the name herein suggested for it, as the central starting point of a nerve path which then descends by way of the bulb, the cord and the splanchnic nerves to the kidneys.

4. That the experimental data recorded by Camus and Roussy and others are accounted for by the inhibition or arrest, as a result of lesions practised by them or the pathological sequels of such lesions in the tuber cinereum, of the physiological impulses through the hypophyseorenal path to the vessels of the kidneys, thus causing passive dilation of these vessels, abnormal excitation of the renal cells by the excess of arterial blood thus permitted to reach them and as end result, polyuria or diabetes insipidus.

5. That the beneficial effects of posterior pituitary preparations are accounted for, not by a supposed secretion or hormone in these products, since the actual existence of such a secretion as a physiological entity has never been demonstrated and is controverted by many facts, but by the recognized pharmacological property of these preparations of causing constriction of the arterioles, thus counteracting in the kidneys the dilation of these vessels, which dilation is the cause of diabetes insipidus and polyuria insofar as their relationship with the *hypophyseorenal nerve path*—a term I would also submit as appropriate—is concerned.

REFERENCES.

1. Vincent, Swale: *Lancet*, 1922, 2, 313.
2. Camus and Roussy: *Endocrinology*, 1920, 4, 507; *Jour. de physiol. et de path. gén.*, 1922, 20, 509, 535.
3. Bailey and Bremer: *Endocrinology*, 1921, 5, 761.
4. Bailey and Bremer: *Ibid.*
5. Houssay and Hug: *Compt. rend. Soc. de biol.*, Paris, 1921, 85, 315.
6. Houssay: *Endocrinology*, 1918, 2, 94.
7. Cushing: *Boston Med. and Surg. Jour.*, 1913, 168, 901.
8. Marañón and Rosique: *Trab. de la Soc. de biol.*, Barcelona, 1917, 19, 126.
9. Houssay and Roman: *Prensa méd.*, Argentina, 1917-1918, 4, 284.
10. Marañón: *Neuvas orientaciones sobre la patogenia y tratamiento de la diabetes insipida* Madrid, 1920, p. 106.
11. Dixon and Cow: *Proc. Roy. Soc. Méd.*, London, Sect. Ther. and Pharmac., 1921, 14, 6.
12. Jacobson, C.: *Johns Hopkins Hosp. Bull.*, 1920, 31, 185.
13. Souques, Alajouanine and Lermoyez: *Trans. Third Intern. Congr. of Neurol.*; cited by *Monde méd.*, 1922, 32, 576.
14. Watanabe and Crawford: *Jour. Pharm. and Exp. Therap.*, 1916, 8, 75.

15. Rogers, F. T.: *Proc. Soc. Exp. Biol. Med.*, New York, 1921, 19, 125.
16. McKinlay, C. A.: *Arch. Int. Med.*, 1921, 28, 703.
17. Dixon, W. E.: *Jour. Physiol.*, 1923, 57, 129.
18. Sajous, C. E. de M.: *Internal Secretions and the Principles of Medicine*, 1908, 2d ed., 1, 293.
19. Foster, Michael: *Text-book of Physiology*, Philadelphia, 1895, 6th ed.
20. MacArthur, A. G.: *Jour. Am. Chem. Soc.*, 1919, 4, 1225.
21. Luschka: *Der Hirnanhang und die Schilddrüse des Menschen*, 1860.
22. Müller: *Jenaische Ztschr. f. Natur-Wissen*, 1871, 6, 354.
23. Berkley, H. J.: *Brain*, 1894, 17, 515.
24. Osborne and Vincent: *Brit. Med. Jour.*, 1900, 1, 502.
25. Piersol: *Human Anatomy*, 1907, p. 1107.
26. de Cyon, E.: *Pflüger's Arch.*, 1898, 72, 635.
27. Masay, F.: *l'Hypophyse*, Thèse de Bruxelles, 1908.
28. Pirrone: *Riforma med.*, 1903, 19, 169, 205.
29. Sajous, C. E. de M.: *Internal Secretions and the Principles of Medicine*, 1903, 1st ed., 1, 483.
30. Weed, Cushing and Jacobson: *Johns Hopkins Hosp. Bull.*, 1913, 24, 40.
31. Sajous, C. E. de M.: *Gaz. des hôp.*, 1908, 81, 339.
32. Schäfer, E. A.: *Proc. Roy. Soc. Biol. (Ser. B)*, 1909, 80, 442.
33. Benario, J.: *München. med. Wehnschr.*, 1913, 60, 1768.
34. Sequeira: *Tr. Roy. Soc. Med., Dermat. Sect., Brit. Jour. Dermat.*, 1915, 27, 186.
35. Berge and Schulmann: *Presse méd.*, 1918, 26, 618.
36. Marafion: *Loc. cit.*, p. 58.
37. Simmonds, M.: *München. med. Wehnschr.*, 1914, 61, 180.
38. Neuburger: *Berl. klin. Wehnschr.*, 1920, 57, 10.
39. Sekiguchi: *Ann. Surg.*, 1916, 63, 298.
40. von Meyenburg, H.: *Zieglers Beiträge*, 1915-1916, 61, 550.
41. Globus and Strauss: *Arch. Neurol. and Psych.*, 1922, 8, 53.
42. Newmark, L.: *Arch. Int. Med.*, 1917, 19, 550.
43. Luzzatto: *Sperimentale*, 1918, 71, 405.
44. Chauffard: *Med. Press. and Circ.*, 1920, 110, 142, n.s.
45. Römer, C.: *Deutsch. med. Wehnschr.*, 1914, 40, 108.
46. Lhermitte, J.: *Ann. de méd.*, 1922, 11, 89.
47. Veil: *Deutsch. med. Wehnschr.*, 1920, 46, 558.
48. Leschke, E.: *Ibid.*, 1920, 46, 959.
49. Lecorché and Talamon: *Am. Med. Digest*, June, 1888; cited by Sajous: *Ann. Univ. Med. Sci.*, 1889.
50. Ebstein, W.: *Deutsch. Arch. f. klin. Med.*, 1909, 95, 1.
51. Marinesco, N. W.: *Arch. Orient. de méd. et de chir.*, 1900, 2, 57.
52. Weiszbart, J.: *Lancet*, 1888, 1, 737.
53. Futeher: *Modern Medicine*, Osler and McCrae, 1914, 2, 724.
54. Eichhorn, G.: *Jahrb. f. Kinderheilk.*, 1896, 42, 44.
55. Motzfeldt, Ketil: *Boston Med. and Surg. Jour.*, 1916, 174, 644.
56. Futeher, T. B.: *Johns Hopkins Hosp. Reports.*, 1902, 10, 197.
57. Lépine, R.: *Diabetes Insipidus*; Sajous' *Analytical Cyclopedic of Practical Medicine*, 9th ed., vol. 4, p. 2.
58. Ricaldini: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1922, 46, 1238.
59. Beck, H. G.: *Dystrophia Adiposogenitalis*, *Endocrinology and Metabolism*, 1922, 1, 894.
60. Hamilton: *Canada Med. Assn. Jour.*, 1922, 12, 209.
61. Briand and Rouquier: *Bull. et mém. Soc. méd. de hôp. de Paris*, 1920, 44, 769.
62. Gosset and Gutmann: *Ibid.*, 1921, 45, 1674.
63. Bénard, R.: *Ibid.*, 1922, 46, 553.
64. Sajous, C. E. de M.: *Internal Secretions and the Principles of Medicine*, 1st ed., 1903, 1, 577.
65. Salmon, A.: *Sull' origine del sonno*, Firenze, 1905.
66. Cammidge: *Practitioner*, 1920, 105, 244.
67. Tucker, J.: *AM. JOUR. MED. SCI.*, 1922, 163, 668.
68. Hall, G. W.: *Ibid.*, 1923, 165, 551.
69. Marafion: *Loc. cit.*, p. 122.
70. Sajous, C. E. de M.: *Internal Secretions and the Principles of Medicine*, 1st ed., 1903, 1, 587.
71. Brubaker: *Text-book of Physiology*, 7th ed., 1922, p. 632.

72. Schäfer: Text-book of Physiology, 1900, 2, 728.
73. Mark, I. P.: Acromegaly; a Personal Experience, London, 1912, p. 28.
74. de Cyon, E.: Cited by Richet: Dictionnaire de physiologie, 1900, 4, 131.
75. Sajous, C. E. de M.: Internal Secretions and the Principles of Medicine, 2d ed., 1907, 2, 1001.
76. Farini, Francesco: Gazz. d. osp., Milan, 1913, 34, 1135.
77. Weir, Larson and Rowntree: Arch. Int. Med., 1922, 29, 306.
78. Rees and Olmstead: Endocrinology, 1922, 6, 230.
79. Bell, Blair: The Pituitary, 1919, p. 144.
80. Sajous, C. E. de M.: Endocrinology, 1918, 2, 258.
81. Sweet and Allen: Ann. Surg., 1913, 57, 485.

CEREBROSPINAL FLUID IN ENCEPHALITIS LETHARGICA.

BY HAROLD E. FOSTER, M.D.,

ROCHESTER, N. Y.,

AND

JESSIE REED COCKRELL, A.B.,

BOSTON, MASS.

(From the Department of Pathology and Neurology, Massachusetts General Hospital.)

ALTHOUGH there has been more or less discussion of the sugar content of the cerebrospinal fluid since its presence in normal fluid was established on a sound basis by Nawratzki (1897) and by Denigès (1898), with the confirmatory work of Gimbert and Coulaud (1903), a more specific interest dealing with laboratory investigations as to its quantitative determination and its possible significance in relation to pathological conditions of the central nervous system has developed during the last three years. Evidence of this interest has demonstrated itself in a rather extensive literature, more abundantly from the French workers, giving the results of researches made in quantitating by various methods the sugar in both normal and abnormal cerebrospinal fluids. Since von Economo (1917, at Vienna) reported cases of encephalitis lethargica, many investigators have pursued laboratory methods of approach in studying the disease. The nature of such work was necessarily a physico-chemical study of the cerebrospinal fluid, obtained from cases giving a clinical picture simulating encephalitis lethargica. With a few exceptions, the amount of sugar in the cerebrospinal fluid of encephalitis lethargica has not received its due measure of attention. This has probably been due to the use of qualitative methods which are of slight value and which do not give sufficiently reliable results to determine either the absence or increase of sugar in the cerebrospinal fluid. Consequently, it is purposed here to present quantitative determinations which have been made on fluids from 35 cases of encephalitis lethargica. The diagnosis is

based in each case on both the clinical signs and symptoms and the laboratory results. Two cases were checked by necropsy. The 35 cases are divided into two series. The second series is a sequel to the one presented by Foster¹ from the same laboratory in 1921. The results of both series are identical in obtaining a percentage of sugar above 0.0600 per cent in all but one determination.

Among the very recently reported investigations, the consensus of results coincides with those obtained in this laboratory. Barré,² using the Fehling's-Durand method, regards an elevation of sugar characteristic of both acute and subacute stages of encephalitis lethargica. Bourges, Foerster and Marcandier³ maintain that the sugar content has always been found higher than normal. Also Laporte and Rouzaud⁴ state "hyperglycorachia has been constant in all the cases observed." Dopfer⁵ considers sugar increased in encephalitis lethargica, but not pathognomonic. Additionally, Coope⁶ presents an 82 per cent increase of sugar from tests made on 95 fluids obtained from 11 cases, using the Folin-Wu method. Moreover, Eskuchen⁷ parallels, with a modified Bang method, the results shown here. Thus the evidence given by these investigators supports the findings recorded in Tables I and II.

The data presented offer various points of interest; the point of striking interest tends, however, in both series to be mostly in the results of the sugar determinations. The percentage of amounts above 0.0600 per cent in Table I, is duplicated in Table II. The results were obtained by the same method, Folin-Wu,⁸ in the same laboratory; one set in 1921, the other in 1922 to 1923.

The Folin-Wu method used for the quantitative determination of the amount of sugar in the cerebrospinal fluid is the same as the method for determining blood sugar, excepting a weaker standard solution is used for the cerebrospinal fluid. This is a 0.005 per cent solution of dextrose which gives a more comparable colorimetric reading than a 0.1 per cent used for blood. Foster¹ found that with some fluids the filtrate was cloudy, but it has since been found that such cloudiness may be eliminated by filtering through four filter papers. The results obtained by the Folin-Wu method give lower quantities than the results determined by the Myers and Bailey and the modified Lewis and Benedict methods, as is shown in a comparative study made by Thalhimer and Updegraff.⁹ In this laboratory, the limiting amounts of sugar in cerebrospinal fluid are considered normally from 0.0400 to 0.0600 per cent.

Evidence of the source of the sugar in the cerebrospinal fluid is wanting. The existence of any relation between the sugar in the blood and that in the cerebrospinal fluid has not been established. Foster¹ did not obtain any alteration in the amount of sugar in the blood in the six determinations that were made on cases with sugar in the cerebrospinal fluid above 0.0600 per cent. Yet the opinion

TABLE I.—1921 SERIES.*

Case.	Sex.	Age.	Time since onset.	Fluid.	Cells per 1 cm. (5 per cm. for normal).	Total protein† (40 mg. per 100 cc normal).	Colloidal gold reaction.	Sugar (0.04 to 0.06 per cent normal).	Wassermann reaction.
1	M.	37	2 days	Colorless.	26	80	0011100000	0.0681	Negative.
2	M.	28	4 "		150	50	0000000000	0.0909	Negative.
			9 "		130	28	0114100000	0.1130	Negative.
3	M.	5	4 "		6	25	0122100000		
			9 "		10	26	0000000000	0.0761	Negative.
4	M.	43	1 wk.		14	42	0000000000	0.0700	Negative.
5	F.	40	1 "		18	55	0122210000	0.0810	Negative.
6	F.	29	1 "		90	47	0122100000	0.0674	Negative.
			2 wks.		90	21	0121100000	0.0620	Negative.
7	F.	26	1½ "		45	44	3355410000	0.0731	Negative.
			4 "		12	0.0695	Negative.
8	F.	10	2 "	Clear.	11	25	0122310000	0.0535	Negative.
9	M.	43	2½ "		8	29	0123210000	0.0710	Negative.
10	M.	54	3 "		22	72	445553100	0.0847	Negative.
			5 "		34	61	4443210000	0.0937	Negative.
11	M.	42	...		144	63	0000000000	0.0666	Negative.

* Foster, H. E.: Jour. Am. Med. Assn., 1921, 76, 1300.

† Denis, W., and Ayer, J. B.: Arch. Int. Med., 1920, 26, 436.

TABLE II.—1922-1923 SERIES.

Case.	Sex.	Age.	Time since onset.	Fluid.	Pressure in mm. H ₂ O (250 mm. upper normal).	Cells per 1 cm. (5 per cm. normal).	Globulin†.	Total protein† (40 mg. per 100 cc normal).	Colloidal gold reaction.	Sugar (0.04 to 0.06 per cent normal).	Wassermann reaction.
1	F.	24	3 days	Colorless.	185	0	+	33	0000000000	0.0576	Negative.
2*	M.	74	Few "		216	115	-	47	0001221000	0.0727	Negative.
3	M.	33	1 wk.		168	15	Sl. +	48	0000000000	0.0917	Negative.
4	F.	16	1½ wks.		140	4	-	29	0000000000	0.0928	Negative.
5	M.	30	2 "		150	39	Sl. +	67	0000000000	0.0689	Negative.
			2½ "		100	12	-	58	0000000000	0.0800	Negative.
6	M.	20	2½ "		60	0	-	36	0000000000	0.0701	Negative.
			3 "		120	2	Sl. +	52	0000000000	0.0700	Negative.
7	M.	27	2½ "		100	1	Sl. +	60	1333320000	0.0730	Negative.
8	F.	20	3 "		180	4	+	50	0000000000	0.0720	Negative.
9	M.	43	3 "		...	4	+	47	0000000000	0.0730	Negative.
10	F.	35	3 "		150	7	-	37	0000000000	0.0980	Negative.
11	M.	51	3 "		130	2	-	33	0000000000	0.0740	Negative.
12*	M.	30	3 "		...	4	+	67	...	0.1030	Negative.
13	F.	38	3 "		175	1	-	35	0000000000	0.0719	Negative.
14	M.	36	3½ "		145	34	-	41	0000000000	0.0724	Negative.
15	F.	28	4 "		50	34	+	54	0000000000	0.0707	Negative.
16	M.	26	4 "		...	32	+	51	0000000000	0.0724	Negative.
17	F.	28	5 "		115	7	+	48	0000000000	0.0645	Negative.
18	M.	36	2 mos.		140	2	-	33	0000000000	0.0645	Negative.
19	F.	26	2½ "		50	44	-	40	0000000000	0.0740	Negative.
20	M.	20	3 "		180	5	Sl. +	67	0000000000	0.0500	Negative.
21	M.	19	21 "		250	3	Sl. +	55	1123321000	0.0606	Negative.
22	M.	63	2 yrs.		100	3	+	67	0000000000	0.0714	Negative.
23	M.	23	3 "		120	2	-	45	0000000000	0.0625	Negative.
24	F.	33	4 "		35	2	-	50	1112321000	0.0657	Negative.

* Nos. 2 and 12 confirmed by necropsy.

† Ross-Jones test with saturated sol. ammonium sulphate.

† Denis, W., and Ayer, J. B.: Arch. Int. Med., 1920, 26, 436.

THE RESULTS OF THESE 2 TABLES MAY BE SUMMARIZED
BRIEFLY:

No. of cases.	Pressure over 250 mm. H ₂ O, per cent.	Cell count over 5 per cm., per cent.	Presence of globulin, per cent.	Total protein over 40 mg. per 100 cc., per cent.	Colloidal gold reaction, per cent.	Sugar over 0.06 per cent.
Table I (11)	...	100.0	...	72.8	72.8	91.0
Table II (24)	0.0	41.6	58.3	75.0	16.0	91.0

of the French investigators tends toward a belief that there is a definite relationship existing between the presence of sugar in the blood and in the cerebrospinal fluid. This viewpoint is held by Laporte and Rouzaud,⁴ who obtained a hyperglycemia simultaneously with a hyperglycorachia in cases of encephalitis lethargica. Likewise, Bourges, Foerster, Marcandier³ report "glycemia parallels glycorachia." Dopter⁵ considers the increase of the amount of sugar in the cerebrospinal fluid to be influenced by an increased amount in the blood. Moreover, Polonovski and Duhot¹⁰ report simultaneous changes found experimentally between the sugar levels in the blood and the spinal fluid. In contradiction to the above observations, Eskuchen⁷ fails to note any relation between the sugar of the cerebrospinal fluid and that of the blood. It is obvious that further research work on the source and function of the sugar in the cerebrospinal fluid is necessary.

Another question is whether the amount of sugar obtained in encephalitis lethargica is a true increase or is only a high normal. The following observation favors the possibility of its being an increased amount: In 225 sugar determinations made in this laboratory during the past twelve months the amounts above 0.0600 per cent were all in fluids, which gave other abnormal reactions. The fluids were from cases of a variety of pathological states, as gas poisoning, feeble-mindedness, brain tumor, metastatic tumor of the spinal cord, septicemia and tabes dorsalis. Therefore, the amount of sugar in the cerebrospinal fluid of encephalitis lethargica is not preferred as pathognomonic of the disease. None the less, it is presented as having diagnostic value in the study of laboratory findings.

In encephalitis lethargica, the fact that the sugar content of the cerebrospinal fluid is the most constantly positive laboratory result, the fact that it is the most striking finding in viewing the cerebrospinal fluid as a whole, indicates the possibility of its being useful in the hands of clinicians. In a cerebrospinal fluid, as Case IV in Table II, showing a clear, colorless fluid under a pressure of 140 mm. of water, 4 cells per cm., no globulin, 29 mg. of total protein per 100 cc, no change in the colloidal gold test, and a negative

result in the Wassermann reaction, but *showing* 0.0928 per cent of sugar and with clinical symptoms suggesting encephalitis lethargica, the quantity of sugar is obviously important. This illustrative example is amplified by an analysis of the findings recorded in Tables I and II.

In Table I, the observations were made on fluids from 11 cases, the duration of the disease since onset being from two days to five weeks; although all cell counts are above 5 cells per cm., none the less no one estimation is above 150; and the largest amount of total protein is 80 mg. per 100 cc; the colloidal gold reaction is given in more cases than in Table II. Whereas the percentage of sugar content is exactly the same as that obtained in the results shown in the second table.

A study of Table II shows a record of 24 patients, with the duration since the onset of clinical symptoms extending from three days to four years, on whom clear, colorless cerebrospinal fluid was obtained under normal pressure. The cell-count is in over 50 per cent of the number of fluids below 5 per cm. with the highest count 115. The presence of some globulin in 58 per cent with the quantitative amount of total protein showing an increase over 40 mg. per 100 cc in 75 per cent. The normal range of total protein is considered to be from 15 to 40 mg. in 100 cc of cerebrospinal fluid by the Denis-Ayer method.* The colloidal gold gives a low percentage of reaction, and in cases giving a curve it is one in the "luetic" zone. The fact of interest in the whole picture is the quantity of sugar. This is above 0.0600 per cent in 91 per cent of the fluids studied.

Emphasis should also be placed upon the part sugar in encephalitis plays in separating this condition from tuberculous meningitis. The clinical picture of the two may cause confusion in diagnosis. Observation of the results in the laboratory from a thorough study of the cerebrospinal fluid reveals characteristic differences between the two. These differences show in comparing Table II with Table III:

TABLE III.—TUBERCULOUS MENINGITIS.

Case.	Cells, 1 cm.	Total protein, mg. per 100 cc.	Colloidal gold reaction.	Sugar, per cent.
1	230	118	0001331000	0.0321
2	325	500	0003444210	0.0400
3	200	100	0000455442	0.0100
4	210	77	1123455210	0.0250
5	150	160	0002222200	0.0410
6	485	400	0000000000	0.0364
7	62	138	0000000000	0.0006
8	203	235	0012333110	0.0010
	202	236	0000122100	0.0010
9	106	500	0001122222	0.0010
10	119	190	0000000000	0.0010
11	210	400	0012333210	0.0350

* Denis, W., and Ayer, J. B.: Arch. Int. Med., 1920, 26, 436.

Table III shows the findings in fluids from 11 cases of tuberculous meningitis: The cell count is high, globulin is present, the total protein is increased, the colloidal gold test is inconstant. Again, it is the quantity of sugar that is interesting, for it is the point of greatest divergence between the laboratory results of the two conditions. The amount of sugar in tuberculous meningitis is always low. In Table III, 45 per cent of the estimations are below 0.0010 per cent. This reduction of sugar in the fluid of tuberculous meningitis is confirmed by reports in the literature.¹¹

Likewise, in cases of acute purulent meningitis all accounts reported by laboratory workers agree that there is an even more marked diminution of sugar than in tuberculous meningitis. The number of fluids examined in this laboratory are few, but the results are tabulated for the sake of completeness. (Table IV.)

TABLE IV.—ACUTE PURULENT MENINGITIS.

Case.	Cells, 1 cm.	Total protein, mg. per 100 cc.	Colloidal gold reaction.	Sugar, per cent.
1	6,800	160	0003555400	0.0000
2	2,500	366	0000000000	0.0000
3	3,000	800	0000122321	0.0000
4	13,416	1320	0000000000	0.0000
5	8,000	500	0000111110	0.0000

Finally, it may be suggested that in other conditions, giving no specific test, as the Wassermann reaction in syphilitic meningitis, but showing symptoms that cause confusion with encephalitis lethargica, a quantitative study of the sugar in the cerebrospinal fluid offers a possibility of differential significance. There have been other conditions diagnosed here encephalitis lethargica. From one case a clear, colorless spinal fluid showed 3 cells per cm. 55 mg. of total protein per 100 cc, a colloidal gold curve of 1123210000; both spinal fluid and blood gave negative Wassermann results. The patient developed Jacksonian epileptic convulsions. Another case gave a clear, colorless spinal fluid that had 11 cells per cm. 56 mg. of total protein per 100 cc, a slightly positive globulin test, a negative colloidal gold curve, and a negative Wassermann reaction. This patient had alcoholic poisoning. Both of these cases presented clinical pictures compatible with encephalitis lethargica. These are noted here only in that it seems likely that such confusion might have been lessened by adding to an otherwise careful study of laboratory findings of the cerebrospinal fluid a quantitative estimation of the sugar content. Confusion in diagnosis caused by an "encephalitic syndrome" is noted in the literature. Hassin¹² reports veronal poisoning; Bassoe¹³ a case of brain tumor; and Hamill¹⁴ calls attention to a case of syphilitic involvement of the central nervous system with a negative Wassermann reaction.

A high sugar is not, as has been said previously, pathognomonic of encephalitis lethargica; a normal sugar is, however, obtained rarely; and a low sugar is, within the experience of this laboratory, unknown.

Conclusions. The main points to be considered from a study of the quantitative sugar determinations made on the fluids from 35 cases of encephalitis lethargica are:

1. The determination of the sugar content of the cerebrospinal fluid should be made by a reliable quantitative method.

2. An amount of sugar above 0.0600 per cent was obtained in 91 per cent of the fluids studied, using the Folin-Wu method.

3. Quantitative sugar estimations are valuable in differentiating encephalitis lethargica from tuberculous meningitis and as an aid in other conditions presenting similar symptoms.

4. The amount of sugar present in the cerebrospinal fluid is not pathognomonic of encephalitis lethargica but is of recognized utility in making the diagnosis.

BIBLIOGRAPHY.

1. Foster, H. E.: Jour. Am. Med. Assn., 1921, **76**, 1300.
2. Barré, J. A.: Bull. méd., Paris, 1921, **35**, 366.
3. Bourges, H., Foerster and Marcandier, A.: Compt. rend. Soc. de biol., 1920, **83**, 914.
4. Laport and Rouzaud: Compt. rend. Soc. de biol., 1920, **83**, 392.
5. Dopter, C.: Bull. de l'Acad. de méd., 1920, **83**, 203.
6. Coope, R.: Quart. Jour. Med., Oxford, 1921, **15**, 1.
7. Eskuchen, K.: Ztschr. f. d. ges. Neurol. u. Psychiat., 1922, **76**.
8. Folin, O.: Laboratory Manual, 1922.
9. Thalheimer, W., and Updegraff, H.: Jour. Am. Med. Assn., 1922, **78**, 1383.
10. Polonovski and Duhot: Presse méd., Paris, January, 1923, **31**, 60.
11. (a) Mestrezat, W.: Compt. rend. Soc. de biol., June, 1919, p. 1089.
 (b) Martin, W. B.: Virginia Med. Month., 1922, **48**, 689.
 (c) Schloss and Shroeder: Am. Jour. Dis. Child., 1916, **9**, 1.
 (d) Jouin, A.: Bull. de l'Acad. de méd., Paris, 1921, **80**, 594.
 (e) Parrot, H. W.: Lancet, London, 1919, **2**, 998.
 (f) Moriez, A., and Pradal, P.: Bull. et mém. Soc. méd. de hôp. de Paris, 1920, **44**, 738.
 (g) Prince, A.: Encephale, Paris, 1920, **1**, 384.
 (h) Page, M.: Gaz. d. hôp., 1920, **90**, 171.
12. Hassin, G. B.: Jour. Am. Med. Assn., 1920, **75**, 671.
13. Bassoe, P.: Arch. Neurol. and Psychiat., 1920, **55**, 118.
14. Hamill, R. C.: Med. Clin. North America, 1919, **3**, 67.

A POSSIBLE RELATIONSHIP BETWEEN THE CURRENT OF INJURY AND THE WHITE-BLOOD CELL IN INFLAMMATION.*

BY HAROLD A. ABRAMSON, M.D.,
NEW YORK.

(From the Laboratories of the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York.)

THE study of inflammation has resulted in the formulation of many hypotheses of the causes and the results of the processes present. For the purposes of the experiments upon which this

* Received for publication, July 18, 1923.

paper is based, inflammation is regarded as a process incidental to some injuries in living tissues; more particularly, the congregating of cells in the zone of injury is considered the essential feature. There is inflammation, and there must be present in the tissue where the process occurs some system of factors which brings certain tissue units to the point of injury, and the cells influenced must be able "mechanically" to reach the point of excitation. The questions of how and why the white-blood cell arrives at the point of injury have been widely discussed. Neglecting the teleological attitude, and without going into a discussion of chemotaxis, surface tension, and so on,^{1, 2} which have been offered as possible explanations and which certainly may play a part, this paper, first, will endeavor to offer an hypothesis which will eventually attempt to correlate qualitatively and quantitatively the chemical and mechanical make-up of tissues with the migration of the white-blood cell to some points of injury; secondly, will present some experimental evidence in favor of this hypothesis; and thirdly, in discussion will elaborate upon the first two.

I. The Basis of the Hypothesis. Although all injuries to cells or tissues are not followed by the microscopical picture of inflammation, inflammation is always an expression of injury. When living tissues are injured, whether the fashion be crushing, burning, cutting, or chemical, there ensue the visual and chemical changes which follow such interruptions of normal tissue metabolism. If a living leaf be cut, and non-polarizable electrodes be applied to both injured and uninjured surfaces,³ there is experienced an electro-motive force between the cut and uncut surfaces. Similarly, if a carefully dissected frog's muscle be cross-sectioned, and non-polarizable electrodes be applied in the same fashion, the injured surface becomes electro-negative and the galvanometer's deflection slowly increases to a maximum, after which it suffers a parallel diminution until it eventually disappears. This current of injury varies with the point of application of the electrode upon the uninjured surface, and is not one due to membrane potential phenomena alone, but because of the fact that between the injured and normal tissue there passes when injury is produced, a more or less constant current which varies in intensity as the many factors of tissue and tissue injury do. Uninjured muscles in the resting state are iso-electric; no difference of potential is manifested at their surfaces.^{4, 5}

Hermann, who made the observations noted above, formulated the law which is applicable to all cases, that, "In every injured muscle fiber the surface of demarcation between the living and dead (or rather dying) portion of the fiber is the seat of an electro-motive force toward the living part." Another related fact brought out by this author is that a general rise of temperature increases the strength of this demarcation current up to a certain limit beyond which it decreases again, until it disappears with the onset of heat rigor.

In the same fashion the currents that can be led off to a galvanometer from an artificial cross-section and from any given point of the uninjured longitudinal surface of a nerve increases, and then decreases one-half in two to four hours. But the difference of potential may increase again, and the current regain its original force if a new section is made near the first.⁶ This fact is important because it seems that the strength of the current is not only influenced by temperature at the site of injury, but also the degree of the lesion. The strength of these demarcation electro-motive forces varied from .02 to .03 of a volt in the frog's sciatic nerve, and was equal to .008 of a volt in that of a horse (Biederman). It has been known to exceed .08 of a volt in a frog's gastrocnemius (Du Bois Raymond)⁷

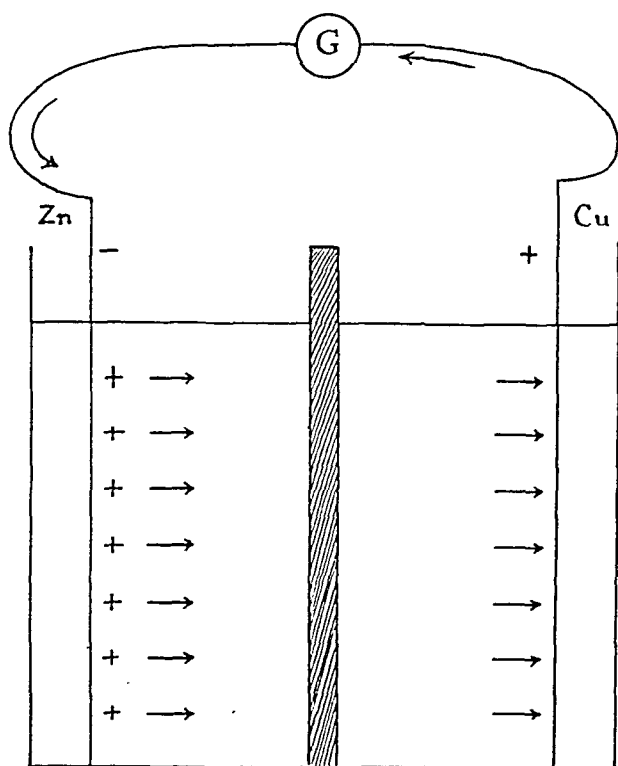


FIG. 1.—Schema to show direction of current in battery.

The significance of these currents of injury in relation to the theory of leukocyte mobility and to inflammation soon to be discussed, is more readily appreciated if the injured tissue and the adjacent normal or nearly normal cells be compared to an electric battery.⁸ From the facts enumerated above it is apparent that injury to living tissues precipitates primarily an increase in chemical activity, one of the manifestations of which is the electrical phenomena observed. This increase in chemical activity may be compared to that which takes place in a battery having zinc and copper plates as electrodes which are immersed in solutions of their respective salts and separated by a porous partition.

1. The pole⁹ on the left becomes negatively charged on account of the departure of positively charged ions from its surface, for this metal, zinc, goes into solution more rapidly than does copper. A current therefore, according to conventional usage, flows from positive to negative through the wire and in the form of migrating ions from positive to negative through the liquid.

2. The difference in potential (E. M. F.) is not affected by changes in the size or shape of the poles or the amounts of the solution, provided the materials are not changed. It is very noticeably altered, however, by changes in the concentrations or the type of solution.

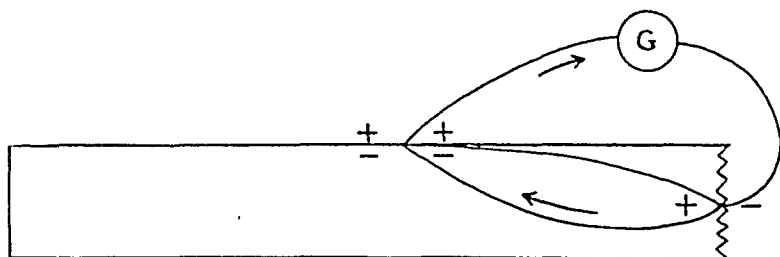


FIG. 2.—Schema to show path of demarcation current.

To resume the comparison of an injured tissue to a battery, the uninjured surface may be considered the positive pole and the injured the negative, the current flowing externally from positive to negative. Internally, the injured tissue may be compared to the immersed zinc plate—the normal to the immersed copper plate and hence the injured area will be electro-positive—the uninjured electro-negative, and the current flow from the injured to the uninjured cells.

If there be between the normal and injured tissues a current flowing which would vary with the type of tissue, degree of injury, temperature of the part, and if in this electrical field there be free cells and injured bloodvessels, the hypothesis, that one of the forces guiding the white-blood cell to the point of injury (and perhaps even playing a dominant role) is the electrical current flowing between the injured and uninjured tissues, is hardly without reason. The concept that the white-blood cell may go toward one pole or another is not new. But the pole to which they migrate has not been settled. For the past thirty years numerous observers have disagreed because the experimental conditions under which they worked were different. Platinum poles instead of non-polarizable electrodes were used; sugar or other solutions held the blood cells in suspension.^{10 11 12} The hydrogen-ion concentration of the medium was neglected. The knowledge of the influence of pH on cataphoresis and proteins in general is a recent acquisition.

The technic to be described obviates as far as possible the errors mentioned above, and although the experiments to be presented

were done *in vitro*, it is fair to draw some parallelism between them and the changes in the living tissue. Unglazed porcelain non-polarizable boot electrodes were set in a glass block 5 mm. apart and ground down so that the level of the electrodes and glass were the same. The apparatus was kept in physiologically normal saline whose pH was about 7.5, approaching that of serum. While on a warm stage at about 100° F., the effect of the passage of a current from a dry cell through human serum containing the cells of the uppermost layer of centrifuged defibrinated blood was observed. The coverslip over the drops was surrounded by paraffin, and thus preventing evaporation, preparations could be studied for hours. A shunted galvanometer recorded the passage of the current and a pole changer was in the circuit.

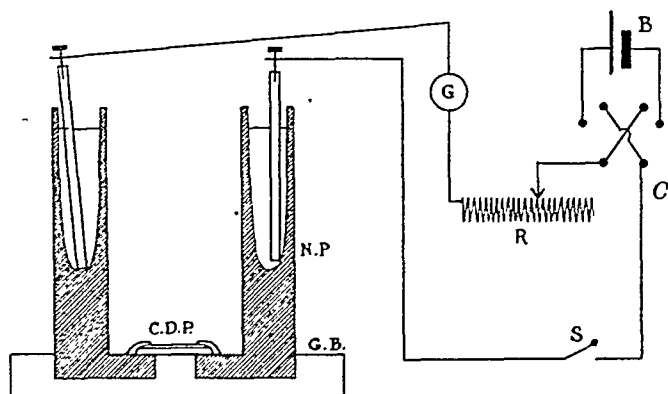


FIG. 3.—Diagram of apparatus; B, battery; C, commutator; C.D.P., coverslip and serum surrounded by paraffin; G, galvanometer; G.B., glass block; N.P., non-polarizable electrodes; R, rheostat; S, switch.

II. Experimental Evidence. The following observations have been made with the technic which was described most briefly in the preceding paragraph.

1. Small lymphocytes, when the estimated difference of potential between the two electrodes is .4 of a volt and the current through the circuit $\frac{1}{25}$ of a milliampère, migrate toward the positive pole with a speed approximately of 15 microns per minute.*

* There are numerous technical difficulties attached to the use of the apparatus described in these experiments. A recent article by Winslow *et al* (Jour. Gen. Physiol., 1923, 6, 177) takes up some of these, and gives rather complete references to the theoretical considerations. The presence of glass particularly influences the speed of migration of particles suspended in a watery medium. Water is electropositive to glass. "That is, the water which moves toward the cathode at the glass surfaces returns toward the anode in the mid-regions of the fluid in the cell. Obviously then, the electrophoretic movement of the particles will be impeded at certain levels in the cell and accelerated at others by the independent movement of the water. In addition, of course, there is the electrical endosmose, due to difference of potential between the particles and the water. The true mobility of the particles is the average mobility of all levels in the cell."

In the experiments of the author there were many mechanical drawbacks, especially the tendency of the white-blood cells to settle upon the glass block, thus preventing an attempt to determine "the true mobility of the particles"—the lympho-

They move faster than red blood cells in the same preparation, pushing them aside and traveling almost in a straight line. When the current is reversed they almost instantaneously change the direction in which they are traveling. All the lymphocytes in the field do not migrate. Those which seem physically able to do so invariably travel toward the positive pole, or, comparing it to the injured tissue, to the electrical equivalent of the point of injury. Although tiny processes seem to be thrown out, there could hardly be said to be much, if any ameboid motion, and the migration could in all probability be considered a result of cataphoretic phenomena.

The speed of migration was not dependent upon the "age" of the lymphocyte. Approximately the same velocity was shown by lymphocytes which were obtained from freshly drawn blood and by those which had been kept on ice for thirty hours or less.

2. Polymorphonuclear leukocytes, under the same conditions, exhibited nothing which could be called a constant direction of migration. The experiments were entirely negative as far as this type of blood cell was concerned. Since unicellular organisms, including ameboid forms, in general under the proper electrical and mechanical conditions move toward one pole or the other,^{13, 14, 15, 16, 17, 18} it should be expected that the movements of the polymorphonuclear leukocyte would also be influenced by the galvanic current. At present a direct analogy cannot be made with the ameba because the observations were not made under known conditions of hydrogen-ion concentration. The effects of glass and of the presence of light, the absence of chemical substances accompanying tissue injury, the need of a stronger current and the mechanical conditions may influence ameboid movement in the leukocyte. In this connection, the effect of glass on the cataphoresis of bacteria,¹⁹

cytes. The cells whose average speed was 15 microns per minute were those which moved. There were also present in the field red blood cells and leukocytes, although an attempt was made to get only white blood cells from the uppermost layer of the defibrinated human blood with delicate capillary pipettes. Many of the lymphocytes, particularly those resting on the glass, exhibited no movement in either direction. Those which did move always moved toward the anode. Hence the figures given in this report for lymphocytic speed under the experimental conditions is not the "true mobility" of the lymphocyte under those conditions, but is an expression of the direction of migration of the lymphocyte, aided in speed, presumably, by the anodal flow of water in the mid-regions of the cell.

In the Helmholtz-Lamb equation,

$$\text{P.D.} = \frac{4 \pi v n}{K X}$$

in which:

n = viscosity of the solution.

v = velocity of the particle in centimeters per second.

K = dielectric constant of the solution.

X = potential gradient.

All electrical units expressed electrostatically, *cannot* be used with the figures reported for the speed of the lymphocytes to determine the potential difference (P.D.) between the lymphocytes and the serum in which they were suspended, because of a lack of knowledge of their "true mobility."

the influence of light on the ameba,²⁰ the change in direction of migration of paramecium brought about by chemical substances²¹ are both interesting and important. For in all probability these factors and the mechanical limitations (*e. g.*, polymorphonuclear leukocytes upon meeting a roughened crack in glass almost invariably ceased to move) play an important role in the failure of the experiments. Even tissue cultures grow in line with a constant current and perpendicular to a conductor.²² The applicability of this work to the repair of tissue injury, to the growth of bloodvessels into granulation tissue and its own formation, is most suggestive when considering the electrical phenomena incidental to injury.

III. The Elaboration of the Theory. Several questions have been asked. Will leukocytes under the experimental conditions react to a stronger current? Are the mechanical conditions present conducive to migration? Does light inhibit their response to the electric current? That is, under the experimental conditions may there not have been many other factors which influence the direction of the leukocytic migration over the pathway described and that observed be a resultant of these forces?

In answer, the following elaboration of the theory is presented purely as speculation based upon the physiology and pathology of inflammation as well as what has been described. In the presence of an acute infection* there are manifested the signs of an increase in chemical activity, and were the demarcation current to be measured, it should be greater than that produced by a low grade inflammatory process. In terms of the current of injury therefore, chemical phenomena are set up in the chronic process which do not produce as intense a current as in the acute process. With a weak constant current are attracted the slow moving lymphocytes; with the stronger current, the greater tissue injury, and perhaps with the production of leukocyte stimulating substances there rush, directed by the demarcation current plus the other factors, the leukocytes and some lymphocytes. As the chemical activity abates and the leukocytes disintegrate, there remains a small but constant current sufficient to maintain a steady lymphocytic migration. And with the further waning of the electrical phenomena, there are fewer and fewer white-blood cells wandering to the site, until with the cessation of the current, the migration ends.

In further support of this point of view is the reaction of the tissues themselves. If they be listed according to the ease with which an inflammatory process be set up within them, it will be found to be a function of the chemical response to injury and hence a function of the demarcation current. That is, connective tissue responds more readily than cartilage to injury, tendon less than connective tissue. The character of chemical make-up of the tissue

* Or any severe injury.

produces a great number of physical and chemical changes in response to injury, the resultant of which is an index of what the demarcation current would be. Experiments by W. C. Clarke and W. C. Woolsey lead one to suspect that hyaline cartilage does not respond to injury by the usual process of repair. A summary of one of the experiments follows: In dog No. 116/85, January 28, 1914, forty-nine days after incision of the cartilage of the humeral head, the surface appeared grossly as if no attempt at repair had taken place. Microscopical examination bore out the gross findings. A "V"-shaped defect into the cartilage, but not through to the underlying bone, revealed no morphological suggestions of repair or change in the surrounding cartilage cells.

If the injury had been one that involved a greater chemical response would the microscopical reaction have been different?

The mechanical limitations to reaction within a tissue like tendon or cartilage also plays its part. Even if the current were strong enough in cartilage, which apparently does not set up a true "chondritis," could the white-blood cell overcome the resistance offered by the poor transits for cellular migration?

The following further experiments would partially determine the appropriateness of the outlined hypothesis.

1. The study of the response of leukocytes and lymphocytes to different currents and electro-motive forces under varying conditions (*e. g.* in the presence of extract of tissue, etc.).

2. The measurement of the demarcation currents of different tissues under standard conditions and their comparison with those used experimentally.

3. The demonstration of the effect of the electric current *in vivo*.

4. The reaction of clinical material treated by the principles of the inflammatory process as cited above.

Summary. 1. A theory is offered that one of the forces guiding the white blood cell to a point of injury followed by an inflammatory process may be the current of injury (demarcation current).

2. With non-polarizable electrodes under stated conditions, small lymphocytes migrate toward the anode which may apparently be compared to an injured tissue focus where inflammation has set up.

3. Polymorphonuclear leukocytes under the same conditions do not consistently go toward one pole or the other. The probable cause of their failure is discussed.

4. The speed of 15 microns per minute manifested by small lymphocytes was the same whether freshly drawn blood cells were studied, or those taken from defibrinated blood kept on ice up to thirty hours.

5. Little if any amoeboid motion was observed during lymphocytic migration.

6. Those tissues which respond most easily with the picture of inflammation to injury, should have the greatest currents of injury, thus correlating the view expressed with the pathological processes.

7. The mechanical and chemical make-up of tissues is stressed as a deciding factor in ease of production of the picture of inflammation.*

BIBLIOGRAPHY.

1. Zinsser, H.: *Infection and Resistance*, MacMillian Co., New York, 1919, p. 85.
2. Wells, H. G.: *Chemical Pathology*, W. B. Saunders Company, Philadelphia and London, 1920, p. 247.
3. Biederman, W.: *Ergebnisse d. Physiol.*, 1903, 2, 264.
4. Hermann, D. L.: *Handbuch der Physiol.*, 1879, 1, 192.
5. Biederman W.: *Elektrophysiologie*, Jena, 1895, p. 274.
6. Du Bois Raymond: *Untersuchungen über thier. Elect.*, Berlin, 1848.
7. Du Bois Raymond: Quoted by Luciani L. (Trans. by F. A. Welby) MacMillian & Co., London, 1915, 3, 75.
8. Waller, A. D.: *Lectures on Physiology*, Longmans, Green & Co., London, 1897, p. 1.
9. Smith, A.: *Inorganic Chemistry*, Century Co., New York, 1915, p. 667.
10. Putter, E.: *Ztschr. Immunitat.*, 1921, 32, 538.
11. Dineur: *Bull. Soc. belge de micro.*, 1891-92, 28, 113, quoted by Putter, E., *Loc. cit.*, p. 539.
12. Lillie, R. S.: *Am. Jour. Physiol.*, 1903, 8, 273.
13. Verworn, M.: *General Physiology*, MacMillian & Co., London, 1899, pp. 455-460.
14. Pearl, R.: *Studies on Electrotaxis I*, *Am. Jour. Physiol.*, 1900, 4, 96.
15. Jennings, H. S.: *Contributions to the Study of the Behavior of Lower Organisms*, Carnegie Institute, Washington, 1904, p. 191.
16. Loeb, J.: *Forced Movements, Tropisms, and Animal Conduct*, J. B. Lippincott & Co., Philadelphia and London, 1918, p. 41.
17. Kosaka and Siki: Quoted by Putter, E., *Loc. cit.*, p. 539.
18. Putter, E.: *Loc. cit.*
19. Putter, E.: *Loc. cit.*
20. Schaeffer, A. A.: *Reaction of Amœba to Light*, *Science*, 1914, 39, 474.
21. Bancroft, L. W.: *The Control of Galvanotaxis in Paramecia by Chemical Substances*, University of California Publications in Physiology, 1906, 3, 21.
22. Ingar, S.: *Reactions of Cells to the Galvanic Current in Tissue Cultures*, *Proc. Soc. Exp. Biol. and Med.*, 1919-20, 17, 198.

PRACTICAL CONSIDERATIONS IN THE MANAGEMENT OF PATIENTS PRESENTING ESSENTIAL HYPERTENSION.†

BY ERNEST S. DU BRAY, M.D.,

INSTRUCTOR IN MEDICINE, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL.

Origin of the Conception of Essential Hypertension. The evolution of instruments for the precise and ready measurement of blood-pressure during the past two decades, combined with the simultaneous introduction of numerous laboratory procedures devised

* The author desires to express his sincere thanks to William C. Clarke, and Arthur P. Stout, of the Department of Surgery and to Professor Horatio B. Williams, of the Department of Physiology, for the aid and criticisms received during the experimental work and the writing of this paper.

† Read before the Medical Society of the State of California, General Medical Section, June 22, 1923.

for the estimation of kidney function, have served to direct attention to a rather large and important group of cases, free from organic changes beyond cardiac hypertrophy and altered vessels, which we have come to designate, essential hypertension.

By this term is meant a state of primary vascular hypertension without the co-existence of demonstrable renal impairment as can be determined by any test of kidney function. Numerous other terms have been applied to this condition, with the idea of defining it more accurately, among the better known of which are, the hyperpiesia of Allbutt,¹ benign hypertension of Vaquez, and the hypertensive cardio-vascular disease of Janeway.

Because of its great frequency, obscure origin and pathogenesis, and its suspected relation to vascular, cardiac and renal disease, interest in this condition has been untiring.

In recent years a modified view of the significance of hypertension has arisen, so that it is no longer regarded as a disease, but rather as a symptom, however, not a constant symptom of any one malady. Hypertension is, therefore, analogous to fever.

What are the Underlying Factors in the Production of Hypertension? Since Richard Bright, in 1836, described the disease which has since borne his name, most physiologists have agreed on one fundamental conception in the mechanism of vascular hypertension. The conception to which I refer, is an increased peripheral resistance in the vascular bed. Today, the chief controversy relates to the manner in which this is produced. Broadly speaking, two essential ideas have dominated the views of clinical pathologists since the time of Bright, the first explained the increased peripheral resistance primarily on a chemical basis; the second, advocated a mechanical origin. In current medical discussions, we find Foster of New York tending to adhere to the supposition of an unknown toxic substance in the circulating blood. This hypothetical substance is assumed to result, either from an infection, or it is the product of a disturbed metabolism. It has a pressor action, causing a vaso-constriction of the arterioles. On the other hand, Moschowitz supports the mechanical conception and contends that structural, sclerotic, arteriolar lesions cause a narrowing of the vascular bed. This anatomical-pathological alteration secondarily gives rise to a compensatory, circulatory reaction, which is manifested by a rise in blood-pressure.

If we carry our analogy between hypertension and fever further, a broader conception of the primary process is suggested. We know that fever can be produced by several causes, chiefly however, by infection. Is it not possible, therefore, that hypertension may have various underlying causes? Christian's careful and prolonged clinical observations have lead him to the belief, that vascular hypertension is a disturbance of the cardio-vascular mechanism, arising from a multiplicity of causes.

A rational therapy of any disease begins with a complete under-

standing of the fundamental cause. Unfortunately, we have not attained this goal in essential hypertension, and for this reason it behooves us to keep our views in the fluid state until the real nature of this condition has been shown. The management of essential hypertension must, therefore, be largely on an empiric basis. Notwithstanding this, there is a growing feeling among medical men interested in this subject, that much can be accomplished in the early cases by preventing premature and unnecessary breakdowns.

What are the Reasons that the Early Management of Essential Hypertension is of Especial Importance? Thanks to the pioneer studies of such clinicians as Sir Clifford Allbutt¹ and the late Theodore Janeway,^{2, 3, 4} we are informed of the progress and the end stages of the hypertensive process. Janeway's extensive and accurate observations are particularly illuminating, and show that death among patients in private practice, occurs in the following ways, arranged in the order of their frequency: (1) By gradual cardiac insufficiency; (2) with uremic symptoms; (3) apoplexy; (4) from some complicating acute infection; (5) in an attack of angina pectoris. For this reason essential hypertension offers an unusual opportunity for the study and control of early disease. A large number of the patients are seen in the incipient stage of the process and if properly managed before too great strain has been imposed on the circulatory apparatus, much can be done to arrest, modify and retard the process.

Proposed classifications of this condition are numerous, but their adoption is hazardous, and particularly dangerous from the standpoint of management, because of the false sense of security they foster.

For clarity and convenience, I will divide my discussion into two parts; the first will deal with the management of the early stage, the second will deal very briefly with the advanced and late stages.

The Early Stage of Essential Hypertension. In the early stage our first duty lies along comprehensive lines, in that it aims to educate the patient in a hygienic manner of living. Fortuitously discovered in the course of routine medical examinations, the majority of the early patients are asymptomatic, and consequently do not consider themselves sick. This fact may lead to half-hearted coöperation, unless the significance and the nature of the process as we know it, is not discussed clearly and frankly, at the time it is discovered. The utilization from the outset of broad psychotherapy is essential, confidence and hope must be inspired and undue fears dispelled. The realization that the height of the blood-pressure, is of far less importance than the conditions which underlie it, must be firmly established.

The Importance of an Intimate Knowledge of the Patient's Daily Life. The important guides in the management of essential hypertension are derived from an intimate knowledge of the patient's

daily life. This is best acquired by a careful history directed to ascertain the type and the surroundings of his work, the amount, kind, and regularity of food, the personal habits, the amount and kind of exercise, the presence of nervous strain and excitement, the amount of recreation, the hours and regularity of sleep, the frequency and length of vacations, and other such details. The importance of these facts as a basis for planning a regime which will be at once practical, acceptable and beneficial to the patient cannot be over-estimated.

Rest and Relaxation. In the early cases complete rest in bed for prolonged intervals is never necessary; however, a short preliminary period of complete rest may be advantageous for patients showing evidence of circulatory strain. A change of occupation may be advisable, but usually this can be avoided by a reduction of the number of working hours per day, or the introduction of rest periods after meals. Complete relinquishment of business is rarely advisable, since loss of interests and physical inactivity often hasten deterioration and may lead to disaster. The assumption of new enterprises with increased responsibilities, should be discouraged. The great value of regular vacations at frequent intervals is often overlooked, but it is one of our most valuable assets in the management of these patients. Regular hours for sleep must be established, and not infringed upon. Errors of refraction, with a resulting eye-strain, are a frequent source of irritation and should be corrected. The morning saline or small doses of mineral oil are often helpful in regulating the bowels. Hurry and worry must be reduced to a minimum, and a mental state of composure and serenity cultivated.

Exercise and Recreation. Systematic exercise is necessary, and particularly important for the maintenance of circulatory efficiency. Out-of-door activities, such as golf, hiking, swimming, horseback riding and gardening are all excellent forms of exercise for the early patients. Besides being less irksome than any form of calisthenics, they have the added psychic value of promoting mental relaxation and diversion. Needless to say, moderation in any form of exercise should be practised and unpleasant symptoms, arising in the course of physical exertion, should remind the patient of his limitations. Strenuous physical training for competitive sports or spasmodic week-end orgies of physical activity are detrimental. In planning the program of exercise, I find Walter Camp's⁵ recent book useful. It contains, among other helpful suggestions, the famous daily dozen exercises, which are readily learned and offer a good substitute to out-of-door diversions, when these are not practical. The acquisition of interests outside of the daily routine is to be encouraged, and for this reason the cultivation of hobbies and tempered enthusiasms play a real part in keeping one fit, and leave less opportunity for useless introspection.

The Problem of Dietary Regulation. Until recently the question of the dietary regulation has formed the main theme in the discussion of the management of these patients. This has resulted from our inability to divorce the nephritic problem of therapy from that of essential hypertension. In my experience no rigid restrictions in the diet are necessary in the early cases, except in those who habitually abuse food. Monotonous and limited diets work a real hardship on patients with this condition, and they are not necessary. Certainly the extremely low-total caloric, low-protein diets which were formerly advocated, now seem undesirable. In general, the patients who are definitely overweight in proportion to their height, as determined by some simple formula for the estimation of ideal weight, should be slowly reduced: (1) By a limitation of the total diet; and (2) by a sharp reduction of the fat component. Patients who are underweight, and in my experience they are almost as numerous as those who are overweight, despite the present-day impression, these patients should be built up by additions in the fat and carbohydrate components. It has been established by Benedict⁶ and his co-workers, that diets of low total caloric value reduced the systolic blood-pressure, but when they were used over prolonged periods, the resulting undernutrition brought about a secondary anemia, and a diminished vitality. The patient, therefore, paid the price of a lessened efficiency, if the goal was reached by undernutrition.

The diet that I find the most satisfactory has the following characteristics: It is simple, well-balanced, contains no more protein than the actual needs of the patient (0.8 gm. to 1 gm. of protein per kilo of body weight), of sufficient caloric value for the energy requirements (2000 to 3000 calories per day), easily digestible, suitable to the powers of mastication of the individual, and is free from excess of meat extractives, condiments and salt.

The method of prescribing a diet based on the foregoing principles, is somewhat as follows: The articles of the diet and the amounts which are to be allowed for the total twenty-four hour period, are checked on a specially prepared diet card containing lists of all the ordinary foods and their proportion of protein, fat and carbohydrate. In this way fairly wide latitude in the choice of foods of approximately the same food value can be allowed. The method is so simple and practical, that the patient soon acquires a sufficient knowledge to use the diet card intelligently, with little supervision.

Sodium Chloride. The question of sodium chloride is the *bête noire* of the present day management of essential hypertension. The restriction of salt in nephritis with edema is a well-recognized procedure, first proposed by the French investigators, Widal and Javal,^{7, 8} in 1903. In 1920, Allen⁹ in this country, advised a rigid salt-free diet for some cases of essential hypertension. In this condition he found the chloride threshold was high, and he suggested

that, "These patients purchase their apparent efficiency of salt excretion at the price of an abnormally high-blood salt and an increased blood-pressure." On the basis of the findings in a limited series of hypertensive patients, notwithstanding certain clinical contraindications of chloride privation, Allen maintained that a rigid salt-free diet brought about a reduced blood-pressure, relieved subjective symptoms, diminished the danger of apoplexy and possibly checked the progress of the condition. In a recent paper,¹⁰ he reaffirms the foregoing statements, and adds, "It is a scientific fact that a relation exists between the chlorides and vascular hypertension." Mosenthal,¹¹ Christian,¹² and others do not agree with Allen, nor have they succeeded in influencing the blood-pressure by salt restriction. During the past two years, in work in the Clinic and with private patients, I have used salt-poor diets, which contained approximately 2 to 3 gms. of salt per twenty-four hours. In many cases, remarkable symptomatic results were noted following the restriction of salt, particularly in the alleviation of the characteristic morning headache, so common in this condition. No effect, however, has been found on the blood-pressure, even after prolonged periods. It has been suggested that the reduction in the fluid intake and food consumption, which follows salt restriction, is connected with the relief of symptoms. The whole problem of salt metabolism awaits further investigation and until this is forthcoming, final judgment on the advisability of salt restriction in essential hypertension, had better be suspended.

Physiotherapy, Hydrotherapy, Electrotherapy, Massage. The bathing habits of patients, with early hypertension, need not be modified. Hydrotherapy is a valuable adjunct to diet restriction and exercise, in weight reduction cures, and may be utilized for this end.

It is generally accepted that the high frequency current will produce temporary reduction in the blood-pressure with an accompanying relief of symptoms. I have had no experience with its use, but I see no objection to its employment for the symptomatic benefit it may afford, provided its administration is carried out by physicians with the special knowledge which is necessary.

Massage is another measure of physiotherapy most useful in elderly patients with vascular changes.

Infection, Syphilis and Tobacco. In the preliminary survey of cases of essential hypertension, local foci of infection in all regions (teeth, tonsils, paranasal sinuses, and prostate, etc.), should be noted. Although no direct relationship has been established between focal infection and vascular hypertension, nevertheless, I believe these foci should be gradually and carefully eradicated. I have been lead to this opinion for two reasons; in the first place, it is urgent to maintain the general resistance of these patients; and in the second place, it is important to protect the cardio-vascular-renal system from added strain or damage from infection. Ophüls¹³

has recently pointed out the importance of the presence of chronic septic infections to injury of the arteries, and to the development of arteriosclerosis; however, no direct relationship has been proved between vascular hypertension and arteriosclerosis.

It is surprising how well these patients with vascular hypertension stand anesthesia and surgical trauma, particularly when a short period of preparation has preceded the surgical procedure.

Syphilis, as far as we know, plays little or no part in the production of essential hypertension, in spite of its well-known predilection to arterial damage. The incidence of syphilis is found to be exceptionally low in hypertensive statistics.

The use of tobacco is best greatly curtailed in all cases, but positively interdicted in those individuals who present evidence of especial hypersensitiveness to it, such as tachycardia and cardiac irregularities.

Drugs and Organotherapy. We have no drugs which directly influence the course of hypertension. Digitalis, to which I will refer more fully later, may be used effectively at times in the early cases, that are beginning to show circulatory strain. Short courses of this drug, combined with rest in bed, should not be withheld until the heart has decompensated.

Insomnia and nocturnal restlessness must be controlled, and I know of no better sedative for this purpose than one which is less commonly used now than formerly, I refer to chloral hydrate, whose action besides that of a central nervous system depressant, is an excellent vasodilator. In therapeutic doses, it is not a cardiac depressant, as is sometime thought. Fifteen to 20 gr. of this drug, taken with warm milk at bedtime, will usually assure the patient of a good night.

The nitrites, except for their use in the vascular emergencies that occur in hypertension, are of no value. Potassium iodide, except in cases with a suspected luetic infection, or advanced arteriosclerosis, is useless. Organotherapy, with the various endocrine products in essential hypertension, has no scientific basis.

The Management of the Advanced and the Late Stages. The advanced stage of essential hypertension is characterized by both subjective and objective findings. Symptoms have appeared and demonstratable physical changes are apparent in the cardiovascular system. Cardiac hypertrophy, thickened arteries, and an accentuated aortic second sound are almost always present. In spite of slight urinary findings the renal function remains comparatively good. The clinical picture at this stage of the process may remain indefinitely, *in statu quo*, and management requires no special measures beyond those outlined already for the early cases.

The Three Important Complications of Advanced Essential Hypertension. There are, however, three important complications that may arise at any time during this period; namely, circulatory insuffi-

ciency, threatened cerebral hemorrhage (a sudden rise of blood-pressure, the so-called hypertensive crisis), and gradual renal insufficiency accompanied by the symptoms of uremia. The serious nature of these complications demands prompt attention.

Management of the Myocardial Insufficiency Secondary to Long-standing Hypertension. The presence of a flagging myocardium will be no surprise to the physician in the well-studied case. Its management requires rest in bed, reduction in diet and fluid intake, and digitalis. The Karrell^{14, 15} diet, or a modification of it, serves to reduce the food and fluids. Violent purging should be avoided and the bowels moved with one of the vegetable cathartics or by enema.

The Use of Digitalis. The use and action of digitalis in this condition deserves special consideration. In spite of the fact that myocardial insufficiency secondary to prolonged hypertension, is seldom of auricular fibrillation variety, digitalis is of great service.^{16 17} If the picture of chronic passive congestion of the viscera and edema has developed (the so-called high blood-pressure stasis complex, as Elliott¹⁸ terms it), the action of digitalis, through a redistribution of the blood from the venous to the arterial side of the circulation, is often dramatic in its promptness. The common statement that a dangerous increase of blood-pressure follows the administration of digitalis, is a myth not founded on clinical facts. Eggleston¹⁹ has shown that digitalis has little influence on the systolic blood-pressure in either way, that it tends to produce a significant reduction in the diastolic and more decidedly, to produce a material increase in the pulse-pressure.

In the presence of good kidneys,²⁰ the skilful use of short courses of diuretics, such as theocin, may be effective in increasing the eliminative activity of the kidney.

Venesection of 500 to 800 cc of blood should be considered, particularly in the cases where the circulatory apparatus appears to be primarily at fault, and the kidneys in a comparatively good condition.

Threatened Cerebral Hemorrhage and Renal Insufficiency with Uremia. Threatened cerebral hemorrhage requires complete rest, an ice-cap, vasodilators, sedatives and possibly lumbar puncture.

The progression of cases of essential hypertension to gradual renal insufficiency, with the retention of nitrogen, and eventually to the development of the picture of uremia, is no rare sequence of events. The management of this condition is beyond the scope of this paper and is more appropriately considered with the subject of chronic nephritis.

Summary. It appears that the management of individuals manifesting essential hypertension is best planned on broad lines, tentatively accepting the postulate that the process results from a disturbance of the cardiovascular mechanism incited by several

underlying conditions. Bad heredity, unhygienic living, excessive mental and physical strain, and infection, may all play a part. A régime for each case should be based on a careful study of the individual's daily life and habits. The readjustment of the manner of living should take into consideration the patient's work, food, exercise, recreation, interests, etc., and all obvious faults corrected. The large number of early cases observed in comparatively young people, offer an unusual opportunity in preventive medicine, since much can be accomplished by simple measures without enforcing a life of invalidism upon them. The fact that over half of all cases of essential hypertension eventually die of some form of circulatory disease, emphasizes the paramount importance of protecting the cardiovascular system from any unnecessary strain and supporting the heart as the emergencies arise.

BIBLIOGRAPHY.

1. Allbutt, C.: Diseases of the Arteries including Angina Pectoris, Macmillan Co. (New York and London), in two volumes, 1915.
2. Janeway, T. C.: Arch. Int. Med., 1913, **12**, 755.
3. Janeway, T. C.: Johns Hopkins Hosp. Bull., 1915, **26**, 341.
4. Janeway, T. C.: AM. JOUR. MED. SCI., 1906, **131**, 772.
5. Camp, W.: A Handbook of Health, and How to Keep It, D. Appleton & Co. (New York and London), 1920.
6. Benedict, T. C. et al: Human Vitality and Efficiency under Prolonged Restricted Diet, Carnegie Institute, Washington, Pub. 280, 1919.
7. Widal, F. and Javal, A.: Jour. de physiol. et de path. gén., 1903, **5**, 1107.
8. Widal, F. and Javal, A.: Jour. de physiol. et de path. gén., 1903, **5**, 1123.
9. Allen: Jour. Am. Med. Assn., 1920, **74**, 652.
10. Allen: Med. Clin. N. A., 1922, **6**, 475.
11. Mosenthal, H. O.: Med. Clin. N. A., 1922, **5**, 1139.
12. Christian, H. A.: New York State Jour. Med., 1921, **21**, 292.
13. Ophüls, W.: Arteriosclerosis, Cardio-vascular Diseases, Stanford University Pub. (Calif.), 1921, p. 102.
14. Osborne, O. T.: Disturbances of the Heart, Am. Med. Assn. (2d Edition), 1916. (See page 211).
15. Goodman, E. H.: Arch. Int. Med., 1916, **17**, 809.
16. Janeway, T. C.: Arch. Int. Med., 1914, **13**, 361.
17. Robinson, G. C.: The Therapeutic Use of Digitalis, Medicine, vol. 1, pp. 1-137. (See especially page 58).
18. Elliott, A. R.: Jour. Am. Med. Assn., 1921, **76**, 1467.
19. Eggleston, C.: Jour. Am. Med. Assn., 1917, **69**, 951.
20. Christian, H. A.: Med. Clin. N. A., 1921, **4**, 1639.

LEUKEMIA: REPORT OF AN ATYPICAL CASE.

BY BENJAMIN GUTMANN, M.D.,

NEW BRUNSWICK, N. J.

LEUKEMIA is a disease about which much has been written and about which there are still many perplexing problems. It is not a new disease, but, since it was first recognized by Hughes Bennett,

and Virchow in 1845, the cause has never been discovered. The similarity, especially in the acute form, to an infection has been noted many times, and is the theory most credited as to the cause, but, in spite of much painstaking work, as for example, that of Dr. John F. Anderson and others, no one has been able to correlate these conditions. Circulating malignant tumor and a blood condition, resulting from and connected with myeloma, are other theories.

Obscure as the etiology of this disease may be, the recognition of the usual typical case is comparatively easy, and the purpose of this paper is not a discussion of those types. Since Ehrlich's classification of the white cells, and with the introduction of polychrome stains, much has been learned in the way of differentiation and separation of this disease into varieties and types.

Mention is made in various text-books of atypical cases, referring more especially to those presenting elements and characteristics of both chief types, and variations in the total number of white cells found in different cases, particularly those with fewer total white cells than usual. The fact that a fair percentage of cases present elements of both types is now quite generally agreed. Also, that the predominance of one type or another, as well as the total number of white cells, varies with the stage of the disease is well known.

Within the last few years the term "leukopenic leukemia" has arisen. In this condition the total number of white cells may not vary much from the normal, may be either slightly increased or even fewer, and yet constitute one of the varieties of the disease under discussion, its recognition depending upon the presence of abnormal or immature cells or a disproportion between the normal cells, as well as the associated clinical symptoms and physical signs. The term "aleukemic leukemia" has also been applied to this variety. These terms, of course, must be considered arbitrary and, so far as I know, have not as yet found general usage.

I desire to report a case which, I think, will fall into this category, and which, also, had peculiarities that should make it of some interest. At the outset I wish to state that I followed the usual classification and terminology of white cells as I knew it at the time, being aware that methods have been introduced to differentiate immature or abnormal white cells from normal cells. I refer to the oxydase reaction. It has not been proved, nor is it generally recognized that this has an advantage over a good polychrome stain for this purpose. The predominating abnormal, or immature, white cell in the case to be presented is the myelocyte, and in this paper the term will be used to mean those cells of moderate to large-size containing an irregular oval, or indented nucleus with a moderate to large amount of cytoplasm containing granules. No attempt was made to differentiate myelogones and premyelocytes from myelocytes. The identification of these cells as myelocytes

was agreed upon by several men of far greater ability than the writer in such work, who were consultants.

With the addition of the above-mentioned oxydase reaction, there has been added by some a third type of leukemia, namely, monocytic; so-called because of the negative reaction with this stain of a large mononuclear cell occurring in abnormally large numbers in cases having other characteristics and manifestations of the disease. While it is possible that this may constitute a distinct variety, it can easily be seen how perplexities are being added in the study of this interesting condition, and the question arises in our minds whether we are not straining at gnats in attempting so finely to separate and classify phenomena in the blood, which will eventually prove to be only a syndrome of some common cause.

CASE REPORT.—The patient was a man, aged sixty-three years, whose family and past personal history are of no particular importance, except to state that his habits were always good. He was a moderate user of alcoholic beverages and he denied any venereal infection.

His illness had an insidious and indefinite onset, and consisted for the most part of a sense of exhaustion, and easily induced fatigue; abdominal discomfort of an indefinite nature, except for a fairly fixed pain in the left side in the splenic region; nausea after taking food, but no vomiting; eructations; pains in legs; sweats, which he described as "cold sweats," during the night, or early morning hours; severe headaches; soreness in the neck along the border of the sternocleidomastoid muscles. These symptoms had existed for two or three weeks prior to July 20, 1920, when the patient was first seen and examined.

Physical Examination. The patient was a well-developed and well-nourished man of late middle-age, with an expression of depression on his face. His cheeks were flushed, but his color was otherwise good. Head: Sclera were clear; pupils reacted equally and normally; patient was slightly deaf; and the specialist who treated this condition considered it of catarrhal origin with no local inflammation in the ear itself. Mouth: Tongue heavily furred by dark-brown coating; many teeth missing, those remaining apparently sound with evidence of recent dental work; throat showed a chronic pharyngitis; anterior nares normal. Neck: Along border of the sternocleidomastoid muscle there were many palpable nodes of varying size, apparently tender on pressure, which felt like enlarged lymphatic glands; thyroid was not palpable and there were no abnormal pulsations. Chest: Symmetrical, with equal expansion on both sides; heart showed no thrills; apex palpable in fifth interspace in nipple line, with the exception of a slight, soft, systolic murmur at the apex, the sounds were clear and of good quality and there were no abnormal accentuations. Blood-pressure, 158

systolic. Lungs: Anteriorly, resonance and breath sounds normal; posteriorly there was impaired resonance with diminished breath sounds and increased tactile fremitus over the right lower lobe, suggesting an old thickening of pleura; there were many moist crackles at the left base, but no apparent change in resonance. Abdomen: Moderate tympanites; liver reached from upper border of sixth rib to just below costal border; spleen could just be felt on deep inspiration, the area of splenic dulness seemingly increased; no other organs palpable; no shifting dulness in the flanks. Legs showed no edema or varicosities; no enlargement of joints; palpable long bones were smooth; no glandular enlargements other than those mentioned above were felt.

Laboratory Results. The sputum was negative for tubercle bacilli; urine was negative chemically and microscopically, except for a very few pus cells (prostate); blood Wassermann, negative.

Blood examination, July 29, 1920: Blood count: Red cells, 4,580,000; hemoglobin, 85 per cent; color index, 1.1 per cent; no blast cells, poikilocytēs nor anisocytosis. White cells, 11,000 per cm. Differential count: Number of cells counted, 200; polymorphonuclears, 36 per cent; transitionals, 11.5 per cent; lymphocytes, 24 per cent; large mononuclears, 7.5 per cent; eosinophiles, 1 per cent; mast cells, 0.5 per cent; myelocytes (neutrophilic), 29.5 per cent.

PROGRESS AND SUBSEQUENT COURSE. The patient continued under my immediate care from above date, July 29, 1920, until August 9, when he left this city for his summer home. During this period his temperature ranged from 97 to 100.7° F., with daily afternoon rise; pulse, 68 to 92; sweats in the early morning hours were of daily occurrence. Complaints about nausea, and abdominal discomfort became more persistent; the stools were offensive in odor; patient slept poorly, but was about the house part of the day, and occasionally took a short auto ride; exercise of any sort produced great fatigue, and there was occasionally slight dyspnea; pains in the legs and discomfort in the mouth persisted.

Diet, rectal irrigations and appropriate medication seemingly made no impression on the gastrointestinal symptoms.

August 4: A consultant from Philadelphia saw the patient, and agreed with the diagnosis. Further blood examinations at this time were in all essential respects similar to that recorded above. From August 9 to August 24 the patient was out of my immediate care, and under the care of a local physician at his country home. From the nurses' records, which were accurately kept, it appears that the patient grew gradually worse, so that more and more time was spent in bed. The tongue became the seat of actual ulcers; the gums were inflamed; the breath became fetid in odor; headaches were intense and persistent; the glands in the neck increased in size, and became more painful; the abdominal distress increased,

and on one occasion, August 19, he vomited mucus, which contained a fair amount of bright-red blood. At this time a rash appeared on his arms and legs, which afterward proved to be subcutaneous hemorrhage. The patient became delirious. His temperature during this period ranged from 97.6° to 102.3° F. The pulse was from 96 to 132, the temperature remaining elevated most of the time.

August 24: I was called hurriedly to see the patient with the statement that he was dying, and when I arrived I found him with a pulse that was absolutely irregular and uncountable, dyspneic, with great difficulty in swallowing, and covered with profuse cold perspiration; respiration, 32. His body was almost completely covered with large patches, bright red in color, due to subcutaneous hemorrhage. He looked, to all intents and purposes, to be in extremis. He responded to very vigorous stimulation, digitalin 1/25, intravenously every three hours for four doses, and the next day his pulse was 100 to 108, temperature 100° to 101.2° F. and respiration 28 to 32, having tided over what seemingly was a crisis. Stimulation in lesser doses was continued. From this period until September 17 the temperature very slowly subsided, and by the date mentioned became practically normal. The pulse remained rather rapid, usually 100 to 110, and respiration 28 to 36. The hemorrhagic areas gradually underwent resolution, but the digestive disturbances, ulcers in the mouth and headaches persisted. However, the mental symptoms became more and more troublesome. There was mental confusion, muttering often, hallucinations and delusions. These mental symptoms seemed to bear no relation to fever, persisting after the temperature became normal. The glands in the neck had decreased considerably in size during this period, and there was no change in the spleen and liver from that noted in the original examination.

September 25: The white-cell count was: Polymorphonuclears, 62 per cent; lymphocytes, 28 per cent; large mononuclears, 2 per cent; eosinophiles, 4 per cent; neutrophilic myelocytes, 3 per cent; transitionals, 1 per cent.

The mental symptoms persisted and followed no definite trend; the patient was disoriented and frequently rebellious, with hallucinations and delusions. He was often incontinent of urine and feces, and at times refused food, so that feeding became a difficult problem. Otherwise, the most annoying symptoms were the stomatitis and gingivitis. Sleeplessness was marked, and he resisted everything but morphin and hyoscin. The patient still complained of pains in his legs and digestive discomfort, and there was considerable foul-smelling flatus from bowel. His physical condition improved, and he was able to spend part of the day out of bed.

The persistence of the mental symptoms so long after improve-

ment in his physical condition caused much anxiety, and on October 28 Dr. Dercum, of Philadelphia, was called for conference. His opinion was that it was a psychosis due entirely to his disease, and that the prognosis was that of the disease underlying it. He had seen two other cases of like character.

November 4: The blood count was as follows: Red cells, 4,200,000; hemoglobin, 90 per cent. White cells, 5900; polymorphonuclears, 57 per cent; large lymphocytes, 7 per cent; small lymphocytes, 29 per cent; large mononuclears, 1 per cent; transitionals, 3 per cent; eosinophiles, 2 per cent; neutrophilic myelocytes, 1 per cent.

It will be seen that change in characteristics of the white cells had taken place; this was noted in other examinations not recorded here. There was a marked disease in the myelocytes, and a relative increase in lymphocytes, with no change in red cells. This relative lymphocytosis is further increased in a count made on December 18, 1920, which follows: White cells, 6450; polymorphonuclears, 51 per cent; small lymphocytes, 39 per cent; large lymphocytes, 4 per cent; transitionals, 2 per cent; eosinophiles, 2 per cent; neutrophilic myelocytes, 2 per cent. There were no blast cells, poikilocytosis or anisocytosis.

November 9: The patient was able to take an auto ride for the first time, although there was no radical change in his mental condition, and he still required morphin and hyoscin for sleeplessness. His temperature would occasionally reach 99.4 by rectum in the evening.

December 1: The patient was up and about considerably during the day, although he became fatigued very easily; his mind had improved and he recognized his surroundings. Morphin and hyoscin for sleep could be dispensed with.

December 11: The patient was able to take a short walk, and on December 13 he went to the office for the first time. He was still easily fatigued and complained of aching in legs and soreness in mouth, although ulcers in his mouth had completely healed. Improvement continued gradually, and the patient a few months later considered himself entirely well.

Subsequent blood counts were as follows:

January 13, 1921: White cells, 7800; polymorphonuclears, 56 per cent; small lymphocytes, 26 per cent; large lymphocytes, 9 per cent; mast cells, 1 per cent; neutrophilic myelocytes, 7 per cent; eosinophiles, 1 per cent. No blast cells, poikilocytosis or anisocytosis.

There is a slight increase in myelocytes from previous counts, but the relative lymphocytosis also persists.

May 11, 1921: Red cells, 4,340,000; hemoglobin, 85 per cent. White cells, 8700; polymorphonuclears, 57.5 per cent; small lymphocytes, 28 per cent; large lymphocytes, 11 per cent; neutrophilic myelocytes, 3.5 per cent.

September 25, 1921: White cells, 5750; polymorphonuclears, 55 per cent; small lymphocytes, 28 per cent; large lymphocytes, 7 per cent; large mononuclears, 4 per cent; transitionals, 4 per cent; neutrophilic myelocytes, 2 per cent. No nucleated reds.

June 15, 1922: Red cells, 4,850,000; hemoglobin, 90 per cent; no poikilocytosis nor anisocytosis. White cells, 5600; polymorphonuclears, 67 per cent; large lymphocytes, 6 per cent; small lymphocytes, 23 per cent; large mononuclears, none; transitionals, 3 per cent; eosinophiles, 1 per cent; basophiles, none; myelocytes, none. No nucleated red cells.

The treatment in the main was symptomatic. Large doses of red bone marrow and arsenic were given, but what effect this had, if any, I cannot say.

Summary. A case is reported with the following points of interest: 1. Many of the clinical signs and symptoms of an acute leukemia, with a high percentage of myelocytes in the beginning of his illness, with only a slight increase in the total number of white cells.

2. Gradual diminution in the number of myelocytes and slight relative lymphocytosis, with a return to approximately normal of the total number of white cells.

3. Relatively very slight disturbance of red cells and hemoglobin.

4. Occurrence of what might be termed a crisis, following which there was slow, but steady, improvement.

5. A marked psychosis considered to be a consequence of the disease.

6. A complete symptomatic recovery, both mental and physical.

7. Return of blood to normal, or nearly normal.

Conclusions. Notwithstanding the doubt in the minds of many physicians, the blood finding and clinical picture in this case, in my opinion, justify a diagnosis of leukemia of that type spoken of as leukopenic leukemia, and if this is accepted we have a rare instance of recovery from that disease.

THE RELATIONSHIP OF GOITER TO MENTAL DISORDERS.

By HAROLD L. FOSS, M.D.,

SURGEON-IN-CHIEF OF THE GEISINGER MEMORIAL HOSPITAL,

AND

J. ALLEN JACKSON, M.D.,

SUPERINTENDENT OF THE DANVILLE STATE HOSPITAL, DANVILLE, PA.

THE study of the subject of goiter and its relation to nervous and mental disease has received a great deal attention as is shown by a review of the literature. Farrant¹ in a detailed study of the thyroids

in 1000 cases of insanity found the gland often "abnormal," varying from considerable enlargement with hyperthyroidism and exophthalmic goiter to complete atrophy with myxedema and cretinism and holds that disturbance of secretion, whether in the form of excess, deficiency or absence, causes an "altered mental state and this combined with the effect of various toxemias renders the patient insane or liable to insanity from slight mental stress." This is typical of the theories advanced by many writers who would link up the endocrine system and especially the thyroid with the insanities and do so, often quite dogmatically, yet fail to support their claims with convincing proof.

The relation of the thyroid and ovaries to confusional insanity has been considered at some length by Wright.² The author points out that "endocrine disturbance may be the cause of all insanities and probably also of psychoneuroses," and states he has "never seen a case of hysteria with a normal endocrine system," yet fails to show what is the normal or how it is to be determined.

The observations of Raymond and Serieux,³ although made over thirty years ago, seem to us to be logical and sound. These authors, after studying a large number of patients in the French asylums, hold that the psychic disorders of Graves' disease are not specific and may assume any form; that they should be considered apart from the disease and be referred to the morbid process to which they properly belong. These authors feel that the occasional association of Graves' disease and mental degeneration is not always a mere coincidence but can be explained by the hereditary defects that give rise to both conditions.

Barker⁴ calls our attention to the usual neurotic and psychic states seen in exophthalmic goiter, conditions which are familiar to all who see many patients with thyroid disease, and it is true that the state of anxiety-phobia, obsession, etc., are often the symptoms that cause the patient first to seek advice. We agree with Barker that pronounced maniacal and paranoid psychoses occur with thyroid disease, but they are rare and, as a rule, are seen only when there is a psychopathic heredity. A few years ago reports of thyroid disease in dementia precox led in many instances to partial removal of the gland but the procedure has never proven a permanent benefit in any large series of cases. It is the feeling of the authors that, with those patients presenting symptoms of dementia and having associated goiter, thyroidectomy is not indicated and if performed will merely precipitate the mental disturbance.

Hammes⁵ in referring to the work of the English Myxedema Commission states that true psychosis is not uncommon in hypothyroidism, the Commission having found such states in 8 per cent of 109 cases examined. The mental symptoms are usually subacute, and, although melancholia predominates, they may take the form of mania.

McCord and Haynes⁶ noted only 0.5 of 1 per cent of cases with thyroid hyperactivity in their study of the endocrine glands of the feeble-minded. Ramadier and Marchana studied the thyroid glands of the insane patients in a goiter district, not finding a greater incidence of cases among the insane than among the sane. From an extensive survey of a large number of cases in many State Hospitals for the Insane, Woodbury⁷ believes "it safe to say that only a relatively small proportion of hyperthyroid cases actually become insane" and, following a study of 300 thyroid cases coming under his personal observation, states that "none presented any psychoneurotic symptoms of possible thyroid origin.

Massarotti⁸ in an exhaustive study of the mental disturbances of Basedow's disease (a study covering 173 pages with bibliography of 435 references) arrives at the following conclusions:

"1. Every syndrome of Basedow's disease presents some nervous symptoms, varying from a simple restlessness, to mild melancholia, mild excitement and a tendency to assume a hostile attitude toward one's environment.

"2. Not infrequently the course of the disease is complicated by true psychoses the most common being melancholia and mania, but these disturbances rarely affect individuals not predisposed, and are generally observed in persons with nervous or mental heredity.

"3. There is no evidence of a pathogenic relationship between the psychoses of Basedow's disease and the disease itself. Generally the subjects are such as are seriously predisposed, most of them, in fact, give a history of previous mental disturbances in whom the trauma incident to Basedow's disease, emphasizes the existing defective nervous system.

"4. In most cases the patients have attacks of mania or melancholia prior to Basedow's disease, which, rather than causing new symptoms, arouses a latent condition."

The Survey at Danville. The authors feel that they are indeed fortunate in having available opportunities, data and facilities especially favorable for a comprehensive study of this subject.

Danville and its vicinity has long been known as a goiter belt. Situated in this field and in the same town there are two hospitals with two distinct classifications of usefulness. The State Hospital is devoted exclusively to the care of mental cases, while the George F. Geisinger Memorial Hospital is a general hospital. To each of these hospitals are admitted patients presenting many interesting types of goiter. The State Hospital offers excellent facilities for the study of goiter and its relation to the psychoses. The George F. Geisinger Memorial Hospital offers an opportunity for the study of the nervous manifestations associated with the many types of goiter in patients who are not mentally deranged.

CASE STUDIES.—A review of the patients at the State Hospital revealed 59 cases of goiter in a total population of 1647. Of this

number 49 were females of the total census of 804 female patients, while there were 10 male patients in a total male population of 843.

In the study of the cases, an effort was made to determine: (1) The relationship between the beginning of the menses, first recognition of the goiter and the development of the mental condition in the female cases and the relationship of puberty, the time of the appearance of the goiter and the mental condition in the male cases; (2) the distribution of goiter among the various psychoses; (3) the types of psychoses to ascertain if possible the presence of a group of symptoms which might be noted in these cases as especially characteristic complications of goiter; (4) if thyroid dysfunction were present.

To determine the general relationship between the beginning of the menses, the goiter and the insanity, questionnaires were forwarded to the reference of each female patient. The replies to these were not satisfactory and the information taken as a whole was not very illuminating while in many instances no replies were received; some were returned unclaimed; many contained no information that would bear any relation on the appearance of these conditions; many stated when the menses began but no information was given as to when the goiter developed; four gave the ages when the goiter was noted, but contained no information relative to the menses; nine replies, however, contained some information which is tabulated as follows:

TABLE I.—AGE AT WHICH SIGNS APPEARED.

Menses.	Goiter.	Insanity.
15	30	30
15	49	From birth
16	Half grown	29
13	15	From birth
15	26	29
12	16	34
11	From childhood	42
14	20	28
15	Some time ago	26

In 4 cases the age when the goiter was first noticed, as well as the date of insanity, were given.

TABLE II.—AGE AT WHICH GOITER AND INSANITY APPEARED IN FEMALES.

Goiter.	Insanity.
Over 30 years	From birth
Some years ago	40
55	55
49	39

In the male group the replies were as follows:

TABLE III.—AGE AT WHICH GOITER AND INSANITY APPEARED IN MALES.

Goiter noticed.	Insanity.
No definite date, but noticed prior to insanity	25-26
20	25
18	24
40	44
54	44
Not noticed	23-25
Not noticed	30
Not stated	43

Although the number is too small to draw any conclusions, the goiter when noticed in all cases, save 1, developed prior to the mental condition.

TABLE IV.—SUMMARY OF FEMALE GOITER CASES.

1. No. of Cases, 49.

2. *Classification of Psychoses:*

Manic depressive:		
Manic	9	} 17
Depressed	6	
Mixed	2	
Dementia precox:		
Hebephrenic	6	} 12
Catatonic	4	
Paranoid	2	
Epileptic psychoses		2
Psychosis with mental deficiency	7	} 14
Mental deficiency without psychosis	7	
Melancholia		2
Paresis		1
Psychosis with cerebral syphilis		1
Total		49

3. *Classification of Types of Goiter with Respect to Type of Psychoses:*

Manic depressive:		
All types		All cases of the adenomatous type
Dementia precox:		
Adenoma	10	
Colloid	2	
Epileptic psychosis:		
Colloid	2	
Mental defectives:		
Adenoma	11	
Colloid	3	
Melancholia:		
Adenoma	2	
Paresis:		
Adenoma	1	
Psychosis with cerebral syphilis:		
Colloid	1	

The adenomatous type of goiter predominates. Of the 49 cases, 41 are of this variety. None of the patients exhibited systemic evidences of toxemia and no goiters were of the hyperplastic type of true Graves' disease.

TABLE V.—SUMMARY OF MALE GOITER CASES.

1. No. of cases, 10.
2. *Classification of Psychoses:*

Manic depressive:		
Manic	2	} 3
Depressed	1	
Dementia precox:		
Hebephrenic	4	} 5
Paranoid	1	
Psychosis with mental deficiency		2
Total		10

3. *Classification of Types of Goiter with Respect to Psychoses:*

Manic depressive:		
All types		All cases of the adenomatous type
Dementia precox:		
Colloid	4	
Adenoma	1	
Mental defectives		All of the adenomatous type.

In but 1 case was there any evidence of goiter in the ancestry. None exhibited evidences of hyperthyroidism nor were any of the goiters of the hyperplastic type.

DISTRIBUTION OF GOITER TO THE PSYCHOSES. Tables IV and V summarize the types of psychoses as well as the types of goiter found. Of the 49 female cases studied, 17 represented the manic-depressive group (manic 9, depressed 6, mixed 2); dementia precox 12 (hebephrenic 6, catatonic 4, paranoid 2); epileptic psychosis 2; psychosis with mental deficiency 7, mental deficiency without psychosis 7 or a total of 14 in the defective group; melancholia involution 2; paresis 1 and psychosis with cerebral syphilis 1.

It should be noted in these tables that goiter was most frequent in the manic-depressive group and in those suffering from dementia precox and mental deficiency. The value of this fact is lessened, however, when we consider that these groups represent the highest percentage of the population of any mental hospital. Nevertheless, it is interesting to note the absence of goiter in the senile psychoses and the low percentage in the epileptic psychoses, both of which represent also a rather high percentage of the hospital population.

In this group of 49 female cases, the adenomatous type of goiter was found in all the manic-depressives; dementia precox shows: adenoma 10, colloid 2; epileptic, colloid 2; mental defectives,

adenoma 11, colloid 3; melancholia involution, adenoma 2; paresis, adenoma 1; psychosis with cerebral syphilis, colloid 1.

The most striking feature is the prevalence of the adenomatous type in the manic-depressive group, in the dementia-precox group and in the mental-defective group, while the colloid type was noted in dementia precox, epileptic psychosis, and cerebral syphilis. It will be seen, therefore, that the adenomatous type of goiter predominates, of the 49 cases, 41 being of this variety. In the entire series of 49 patients there was no evidence of toxemia.

The summary of the male cases as shown in Table V is as follows: manic-depressive insanity is represented in 3 cases, dementia precox in 5 cases, psychosis with mental deficiency in 2 cases. Here again we note that the adenomatous type of goiter prevails in manic-depressive insanity. The colloid type, however, predominates in the dementia-precox group in contrast to the findings in the female cases while the mental defectives show the adenomatous type. Here again, we found a lack of symptoms of toxemia.

STUDY OF THE MENTAL SYMPTOMS. A detailed study of the various types of psychoses, by Dr. H. V. Pike, Clinical and Community Director, shows that the mental symptoms presented in each group fall logically into a classification represented in the tables. The voluminous nature of the reports and the space required for their publication prohibit their presentation in this communication. In studying the cases every care was exercised to eliminate the possibility of error in diagnosis and to determine the possibility of the presence of mental symptoms which would tend to show a possible condition which might be called thyroid psychosis, or a psychosis with symptoms characteristic of thyroid disease. The clinical findings, however, were so distinctly characteristic of definitely recognized psychoses, each case falling into its proper classification, that the possibility of a mental clinical syndrome which might be regarded as characteristic of a psychosis associated with thyroid disease was ruled out. Neither were there any distinct physical findings indicating a general systemic disease associated with the enlarged thyroids of these patients.

THYROID DYSFUNCTION. Every effort was made by means of clinical studies, physical examinations and basal metabolic investigations to determine the presence or absence of thyroid dysfunction. With the means at our command, we were unable to find anything in this group of cases which would lead us to say that there was any marked evidence of disturbance of thyroid secretory function. We are led to believe, therefore, that the presence of thyroid enlargement can only be regarded as coincidental having no definite bearing on the mental disease from which the patients suffered.

The writers are not unmindful that, while the cases studied in detail in this presentation show no relationship between the thyroid and the mental disorder present, the general practitioner will fre-

quently find cases of exophthalmic goiter with certain associated neurotic or psychoneurotic manifestations. Such cases, however, do not represent a true psychosis.

It is interesting to note that at the State Hospital this type of patient, that is the neurotic or psychoneurotic patient with goiter, has not been admitted. The reason for this may be that these mental manifestations are due to toxemias which are modified by or cleared up under general hospital treatment. It would seem, therefore, that before we can associate any definite relationship between thyroid dysfunction and a true psychosis, we must have all the clinical symptoms associated with the psychosis, the definite clinical symptoms of thyroid dysfunction and a positive disturbance of the metabolic rate.

General Hospital Observations. It was important, in connection with this study, to make a survey of the various types of goiter that are constantly being admitted to the Geisinger Memorial Hospital, a general hospital, situated in the same town with the State Institution in which the mental cases of this series are being treated and drawing its patients from the same field. Both institutions are in a section of the country where endemic goiter is common and, while the hospital for the insane has among its 1700 inmates but 59 cases of goiter with an annual admission of not over 2 or 3 new cases, the general hospital has treated over 800 cases in seven years. Diffuse colloid goiters and the so-called "multiple adenomatous" goiter, either with or without hyperthyroidism, prevail with a certain percentage of true exophthalmic goiter. Many of the adenomatous forms are associated with thyrotoxicosis and advanced cardio-renal disease rendering this form one of the most important under treatment, not only numerically but also because of the advanced and serious nature of the complicating degenerative changes with which such patients are usually afflicted. Of the hundreds of patients admitted for surgical operation (and practically all other than patients with small colloid goiters are so treated) only an extremely small number have shown evidences of mental aberration. This has been especially true with the patients with the nodular forms of goiter and, even with patients suffering from the most profound toxemia of true exophthalmic goiter, although there may be nervousness and mild excitement, there has been very rarely true insanity. Large diffuse colloid goiters are occasionally seen in imbeciles, such conditions often being present among several of one family, but with these patients there has usually been an easily traceable hereditary taint and the goiter has existed merely as an accompaniment and surely not the cause of the mental inferiority. Occasionally patients with severe toxemia of exophthalmic goiter evidence a mild, transient, delirium but this has occurred with less than 1 per cent of our cases. Two patients among over 800 developed, several weeks after bilateral

resections, severe and uncontrollable mania with death ensuing: Both had been operated on for relief of large multiple adenomatous goiters without associated systemic symptoms, the type of gland necessitating extensive resection. The symptoms later developing surely were not those of a crisis of acute postoperative hyperthyroidism, nor did they in any degree resemble those of tetany. Many others among our patients have had as complete resections and have passed through an uncomplicated convalescence so that the cause of the grave results in the 2-cases mentioned has been a matter of conjecture with no satisfactory solution.

The neuroses of adolescence are frequently associated with diffuse colloid enlargements but that such mental states are the result of thyroid dysfunction is very improbable, and, surely in a section of the country where at least 15 per cent of the young girls have some thyroid hypertrophy, the two conditions can only be considered as coincidental and not as cause and effect. In the general hospital referred to, where the treatment of goiter is proving an important part of the daily work, no insane patients with goiter are being seen while mental disturbances developing in goiter patients under treatment are of the rarest occurrence and have been noted only in the occasional patients mentioned above.

Among the cases of insanity with associated goiter studied in this series at the State Hospital, there have been no examples of true exophthalmic goiter and while a few patients have shown evidences of mild hyperthyroidism as revealed especially by increased basal metabolic rates, the majority have presented no systemic evidences of toxemia. The incidence of the various types of goiter about parallels that of the patients with normal mentalities applying at the general hospital in the same locality, with multiple adenomatous goiter predominating with some diffuse colloids and with a small incidence of true exophthalmics.

So utterly futile has thyroidectomy in the insane cases seemed to be that but little tissue has been available for pathological study, but in the few glands that have been removed in the hope of aiding the patient, the nodular, so-called "adenomatous" forms with the various degenerative changes peculiar to goiter have been revealed and nothing further. Surely from what pathological studies that have been made, no connection between the thyroid as an etiological factor and the mental aberrations have been traceable. We have searched diligently among our insane for a case of definite hyperthyroidism, for, with such a condition present, much possibly could be promised by ligation and resection, but in this search we have been disappointed. It is, however, apparent to us, having under our observation constantly in the two institutions many hundreds of patients both normal mentally and insane, and both with and without associated thyroid disease, that there is no definite relationship between thyroid dysfunction and insanity. Treatment aimed at

the thyroid gland, therefore, with the hope of improving the mental state seems quite illogical.

It is too much to claim that there is a typical Basedow's-psychosis. The mental state of the patient with exophthalmic goiter is of keen alertness, with mild excitement, but not insanity. "Restlessness and irritability are marked symptoms. The patients appear to be markedly stimulated and their movements are semi-purposeful, or even choreiform. Their mental outlook is self-confident and optimistic" (Plummer). Although the most advanced, untreated case may develop a preagonal mania, yet this is seen only as a terminal condition. Surely it cannot be said that the mental disturbances of exophthalmic goiter are specific, as is claimed by some authors. In the patients who present temporary mental disturbances, the latter do not differ from similar complications occurring in other exhausting conditions, such as tuberculosis, nephritis and similar diseases.

There has been a tendency of late to attribute any and all pathological states to disturbances in the organs of the endocrine system and so thyroid excision or thyroid feeding (it seems not to matter which) has been repeatedly urged in the treatment of the feeble-minded.

We believe that colloid goiter, especially endemic colloid goiter of adolescence, is at present passing through that phase of surgical exploitation through which most diseases seem to have to pass at one time or another. The honors which have been handed from the retroverted uterus to the appendix and from the latter organ to the movable kidney and ptosed stomach, are at present shared about equally between monkey glands and colloid goiter.

It is most deplorable that so large a number of unfortunate young people are being subjected to needless and harmful thyroidectomies. The patient who suffers from early psychic imbalance and has an associated colloid goiter is in grave danger when she falls into the hands of the loose thinker who is all too ready to attribute every abnormal state to disturbed thyroid activity. Among our patients in the State Hospital is one on whom one of us had refused to perform a thyroidectomy some years ago, even though pressed to it by the family. The patient at that time presented slight yet significant mental disturbances and possessed a small diffuse colloid goiter. Manifestly there was no connection between the two. A surgeon with large goiter experience later performed a thyroidectomy while in a few months the patient was committed as a clear-cut case of dementia precox.

Wright² has called our attention to the relationship of the thyroid and confusional insanity and melancholia and speaks of the changes taking place in the female after the menopause when the "Mental attitude reverts to a neutral type" when the "endocrines" especially the ovaries and thyroid play an important role. Yet much of

this is pure theory for at the present time no single problem of endocrine physiology has been satisfactorily worked out and the giving of thyroid and ovarian extract to middle-aged women with mental disturbances is but pure empiricism. The extremes to which the present vogue of endocrinology has carried many of us, urged on as we have been by the manufacturers of pharmaceuticals, have caused Marine in despair to speak of the new and struggling science as "endocrinology."

BASAL METABOLISM IN THE INSANE. Ten patients taken at random although chosen from among those thought most likely to show evidences of hyperthyroidism, were referred to the Geisinger Memorial Hospital for basal metabolic determinations. The average results was $+6$ although with 1 patient, on whom a satisfactory reading was obtained, a rate of $+26$ was recorded. Many tests were unsatisfactory because of the patient's refusal to coöperate. One reading of $+50$ was secured from a patient not definitely hyperthyroid, the high rate probably being influenced by the patient's keeping her legs moving rapidly during the entire test. The conclusion is drawn that hyperthyroidism did not exist except in possibly 2 per cent of all the cases and in these but to a very slight degree. The multiple adenomatous type of goiter predominated with an occasional single cyst and a few diffuse colloid goiters. No typical small, symmetrical, parenchymatous gland of true exophthalmic goiter was discovered. Some of the largest goiters we have seen have been noted in the insane and several patients in this series had such massive adenomatous and cystic enlargements that their possessors appeared to support their heads only with great difficulty. None were clinically hyperthyroid. The two largest goiters in the institution were in two middle-aged sisters, one of whom was operated upon for the relief of pressure. The patient recovered satisfactorily but no change in the mental condition was noted and she died several months later from pneumonia.

Conclusions. The close observation of about 800 goiter cases coming to a general hospital for treatment and the simultaneous study of 50 goiter patients among 1700 inmates of a large hospital for the insane, both institutions in the same locality and drawing their patients from the same territory, lead us to draw the following conclusions:

1. That goiter is not, even in a goiterous district, especially common in the insane, rather the reverse, for its incidence in the State Hospital at Danville, Pa., is but 3 per cent.

2. Conversely, insanity is extremely rare among the large number of goiter patients applying for treatment in a general hospital in the same locality, there being no cases of true insanity among the 800 patients studied, the only mental disturbance being in the form of a mild excitement or rarely slight and transient mania, this in but 2 cases.

3. There is, apparently, no definite relationship between goiter and insanity and surely nothing to indicate thyroidectomy in the treatment of the usual insane patient suffering from complicating goiter, unless for the relief of mechanical pressure. Operation, of course, may be indicated if there be accompanying evidences of true hyperthyroidism, but this latter condition is most rare.

4. Neither hyperthyroidism nor hypothyroidism occurs, except very rarely, among the adult goiter patients of the Pennsylvania hospitals for the insane, the greatest number of goiters being of the so-called multiple adenomatous or nodular forms and unaccompanied by systemic disturbances.

BIBLIOGRAPHY.

1. Farrant, R.: The Causation and Cure of Certain Forms of Lunacy, Brit. Med. Jour., 1916, 1, 882.

2. Wright, J. S.: The Relation of the Thyroid to Confusional Insanity and Melancholia, Kentucky Med. Jour., 1919, 17, 271.

3. Raymond and Serieux: Troubles psychiques de la maladie de Basedow, abstract in Rev. internat. de bibl. méd., 1892, 11, 294.

4. Barker, Lewellys F.: Nervous and Mental Symptoms in Exophthalmic Goiter, Med. Press and Circ., 1919, 107, 85.

5. Hammes, E. M.: The Relation of the Internal Secretions to Neurology and Psychiatry, Journal-Lancet, 1916, 36, 449.

6. McCord and Haynes: Dysfunction of the Internal Secretary System, New York Med. Jour., 1917, 105, 583.

7. Woodbury, M. S.: The Psychoneurotic Syndrome of Hyperthyroidism, Jour. Nerv. and Ment. Dis., 1918, 47, 40.

8. Massarotti, V.: I disturbi mentali nel morbo di Basedow, Roma, 1914.

A STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRA OF CEREBROSPINAL FLUID—A NEW TEST.

(PRELIMINARY REPORT)

BY TAKUJI SHIONOYA, M.D.,

TOKIO, JAPAN.

(From the Research Laboratory of Prof. K. Miura's Clinic, Medical Department, Tokio Imperial University.)

A GOOD many methods have hitherto been advocated for the examination of cerebrospinal fluid, but the one which depends upon absorption spectra of ultraviolet rays has never been introduced. I have, therefore, made a study of cerebrospinal fluid from patients suffering from cerebrospinal diseases and from control subjects, all being the in-patients of the medical clinic of Prof. K. Miura. This was carried out at the laboratory of Dr. Yuji Shibata, professor

of the College of Science of the Tokio Imperial University, with the coöperation of Prof. Shibata and Dr. T. Inouye, an assistant to the professor.

Theoretical and Experimental. The appliances necessary for the experiment are emission apparatus, Baly's absorption tube, and Adam-Hilger's quartz spectrograph.

Emission Apparatus. Iron gives an electric arc, lasting two or three hours, because of its high melting point. If the two poles of the electric arc are made of iron clubs, when a 100-volt, 4 to 5 ampère current is passed through the system the iron evaporates in the electric arc heated to incandescence. The white spark of this iron gives a photograph of a special, long, and densely arranged line spectrum. Since each wave length of these lines has been thoroughly explained, and also since iron is comparatively inexpensive, the use of iron is practical.

Baly's Absorption Tube and Quartz Spectrograph. In taking a photograph of absorption spectra, it is advisable to alter the thickness of the layer as long as the concentration of solvents does not exceed a certain degree, rather than to change the concentration of solution each time. For this purpose, Baly's absorption tube is commonly used. The apparatus is constructed of outer and inner glass tubes; the inner tube is inserted in the outer one by means of a gum stopper. The layer can be changed by regulating the inner tube. There is a globular attachment on the top of the outer tube in order to hold the excess of fluid, and a scale on the side indicates the thickness of the layer. Quartz plates pasted on the end of both tubes give forth the spectra about 20 cm. in length, spreading from red to ultraviolet. The fluid to be examined is put into the upper attachment and the inner tube is regulated so as to change the thickness of the layer from 10 cm. to 0.1 cm. Of Baly's various tubes, one 10 cm. in length and 10 cc in capacity is used. It is attached to Adam-Hilger's quartz spectrograph, and by moving the film up and down, a photograph of each spectrum in each layer can be taken on one film.

Quantity of Cerebrospinal Fluid. The quantity needed for this examination is not more than 10 cc, this being the capacity of the tube. Strictly speaking, 8 cc of fluid is found to be sufficient, because in normal fluid the absorption appears in the thickness of 8 cc, and in abnormal, less than 8 cc.

Concentration of Cerebrospinal Fluid: The dilution of the cerebrospinal fluid is not necessary.

Drawing of Absorption Curve. In general, when there are some solvents which absorb ultraviolet rays, the absorption appears as a wide band on the spectrum. By Beer's law,¹ the width of the band changes according to the concentration of solution or the thickness of the layer. When the concentration or the layer is increased, the band becomes wider, and when they decrease, it

becomes narrower, and at a certain point, disappears. This fact enables us to judge the density of the solvents. The location of the absorption would also tell the molecular structure of solvents. In order to know them we have to draw the absorption curve. The

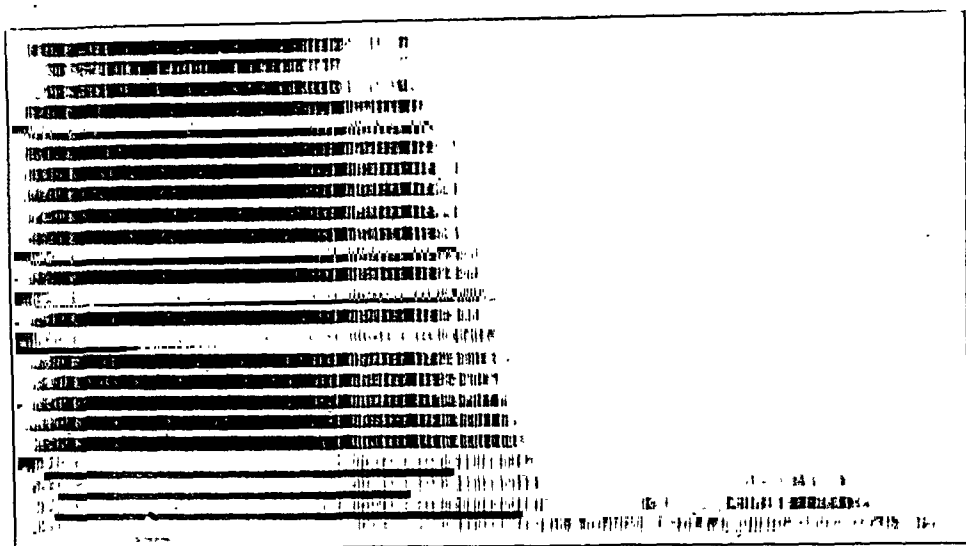


FIG. 1

method of drawing the curve was first introduced by Hartley.² He took a photograph of absorption spectra in various thicknesses of layers, and measured the wave length of the absorption end under the microscope. Taking the wave lengths of the absorption ends as abscissæ, and the widths of layers or concentrations as

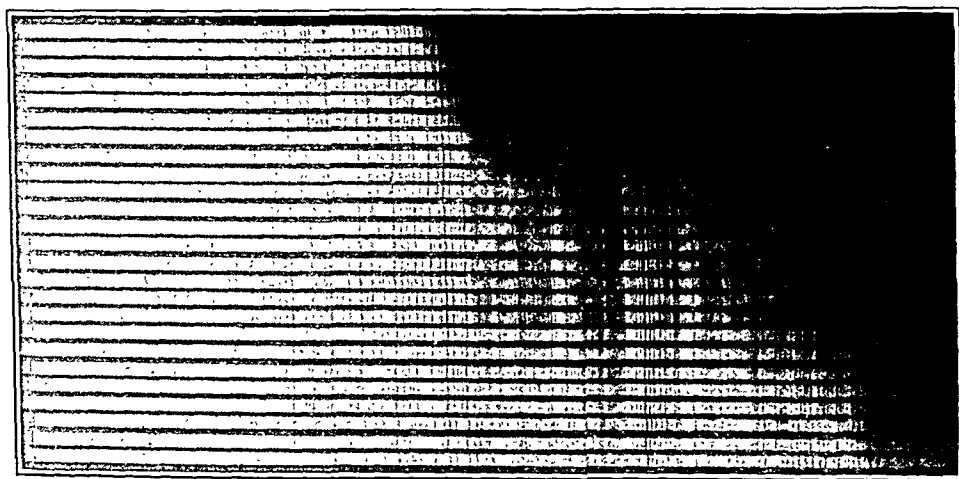


FIG. 2

ordinates, the curve was drawn. This method, however, is not satisfactory because, when the thinnest layer at which the absorption is produced becomes less than 1 cm., the curve would not show the difference of layers. On this account, even if there is the absorption

band, the basis of absorption curve becomes extremely flat and it is difficult to find the center of the absorption band. When the logarithms of the thickness of layers are taken as ordinates instead of the thickness itself, as Hartley later modified the method, the curves shorten at the thick layer in width and elongate at the thin layer, and the variation becomes apparent. When the reverse (it is called wave number) of wave length is taken as the abscissa, instead of wave length, the red ray appears to the left of the ultra-violet, as is seen in ordinal spectrum and is convenient for comparative study.

The cerebrospinal fluid subjected to the above test does not change its chemical composition, neither is the quantity reduced. Therefore, assisted by other known tests of cerebrospinal fluid I have been able to carry out my tests with a limited quantity of the fluid.

History and Pathological Findings of Patients. Ten cases were examined and studied, except two which were considered clinically normal in the cerebrospinal system. The case histories were as follows:

CASE I.—S. K., farmer's wife, aged thirty-one years.

Previous History. Had been healthy, had suffered from no noteworthy sickness, one normal parturition, no venereal diseases.

Present Status. No pathological alterations in internal organs, nervous system, or skin. Wassermann test negative, diagnosed as healthy. On July 20, 10 cc of cerebrospinal fluid was taken.

CASE II.—I. I., farmer's wife, aged thirty years.

Diagnosis. Graves' disease, with apical infiltration of right lung.

Previous History. From the early part of February, 1922, had complained of tired feeling in whole body, palpitation, thirst, and sweating, etc. No venereal diseases. In the middle of February, struma was discovered by a physician. Had had three abortions, and two babies died immediately after birth.

Present Status. Slight exophthalmos, symptoms of Moebius, von Graefe, Joffroy, etc., present. Boston's and Stellwag's symptoms absent. Thyroid gland enlarged, with murmur heard on auscultation. Heart enlarged on both sides; heart-sounds strong, impure; systolic murmurs over heart. Marked tremor of hands. Wassermann reaction of serum positive. Dulness at apex of right lung. On May 19, lumbar puncture performed.

CASE III.—T. M., dealer in pouches, aged forty-four years.

Diagnosis. Tabes dorsalis.

Previous History. When about twenty years of age, suffered from bubo on right side. On February 25, 1922, was run over by an automobile, occiput injured, unconscious for about five minutes. After two or three days felt headache and had paresthesia and

hypesthesia in both hands and fingers. After twenty days, paresthesia noted in planta and toes, and ataxia in walking.

Present Status. Both pupils irregular, reflex to light sluggish, nystagmus present. Ataxia in both hands and feet. Test for Romberg's sign, positive. Internal organs show nothing abnormal. On May 25, lumbar puncture performed.

Three Cases of Spinal Syphilis. CASE IV.—K. K., employe of firm, aged thirty years.

Previous History. Twenty-one years ago suffered from gonorrhea. Though ignorant of being contaminated with syphilis, had had alopecia eight years previously, and when examined three years ago Wassermann reaction was said to be positive. Had had eight arsphenamine injections. His wife had had three abortions. Present ailment dated back to February of this year, when his feet became paretic and walking tremulous. He displayed paresthesia and hypesthesia first in right hand and then in left. These conditions were most marked at the beginning of April but subsided about two weeks later.

Present Status. Facial nerve, vision, auditory organs, etc., apparently normal. Pupils circular, light reflex present. Right foot slightly atrophic. Dorsiflexion of toes, incapable. Negative to Romberg's sign; no ataxia. Periosteal and tendon reflexes of limbs exaggerated, the right being more marked than the left. Clonus of both sides. Tests for Babinski's and Mendel's reflexes, etc., negative. The region below the lower abdomen and radial sides of both hands and forearms hypesthetic. Wassermann test on serum positive. On June 29, lumbar puncture performed.

CASE V.—T. U., greengrocer, aged fifty-five years.

Previous History. When four years of age suffered from smallpox. Denied venereal diseases. Had six children, another dying immediately after birth. Present disease began eight years ago with pain in left hand, followed by paresthesia of right scapular region; two weeks later paresis appeared in left upper extremity and gradually extended to the right upper extremity. From the middle of December of the same year, paresis and hypesthesia were noticed in both feet. The following year he suffered from dull pain in thigh and from dysuria. He had received no specific treatment but had had spontaneous remissions.

Present Status. Cranial nerves show nothing of note. Right pupil normal; left sluggish in light reflex. Internal organs normal. Periosteal and tendon reflexes of upper extremities hyperactive. Knee-jerk and Achilles-tendon reflex hyperactive. Babinski's phenomenon positive. Sense of touch and pain diminished in the left upper arm. Slight ataxia. Paresis of bladder with a feeling of retention after the urination. Frequent urinations. May 27, lumbar puncture performed.

CASE VI.—N. O., employe of firm, aged forty-two years.

Previous History. In September, 1921, showed paresis of left hand, and a few weeks later, dull pain began in left elbow and shoulder, also paresthesia of left upper arm and left hand. In the middle of December, paresis and paresthesia of right hand, also edema of right hand and right upper arm. From January, 1922, on, paresis of both hands grew worse, and in the middle of February appeared in both feet. Paresthesia and pain in shoulders and loins became much worse. A month later, he became incapable of walking and had to go to bed. Since February there have been urinary disturbances. At the end of March, slight atrophy of both hands noted. Early in May, symptoms were spontaneously relieved and patient began to walk again with some assistance. Patient married at the age of thirty-two years, and had four children. Denied venereal diseases. Wife had had no abortions.

Present Status. Pupils normal. Vision, hearing, and facial nerves show no pathological changes. Alopecia. There is a stiffness in neck and consequently movement is restrained. Lymph-nodes in elbows and neck palpable. Internal organs free. Hyperhidrosis of forearms and fingers. Extreme atrophy of muscles. Paresis in upper extremities and a slight tremor of fingers. Tendon and periosteal reflexes of both hands not active. Spastic paresis in both feet. Walking is spastic, paretic, and next to impossible. Knee and Achilles reflexes extremely hyperactive. Ankle-clonus on both sides. Babinski and Mendel-Bechterew's phenomena positive. Wassermann reaction on serum positive. Course of disease: Since June 13, mercury and iodine treatment. On June 19, became much better and was able to walk without assistance. Dysuria and hyperhidrosis disappeared. Cerebrospinal fluid was xanthochromic.

A Case of Brain Tumor. CASE VII.—S. M., cake-dealer's wife, aged thirty-eight years.

Previous History. Married at the age of twenty-two years, and had four children. One child died immediately after birth, and another died of meningitis when five years old. No history of venereal diseases. Grandparents died of tuberculosis and mother of gastric cancer. Present disease began in April, 1921, with difficulty in hearing, and pain in left ear. In September she had seizures of circumscribed headache first in right occipital region, later in left parietal and temporal regions. These seizures lasted for about two hours and would subside after yellow fluid was vomited. At first the seizure occurred once a month but since January, once every four days, at which time paresis started in the lower extremities. In February had frequent attacks of vertigo. Since the onset of the present disease there had been attacks of extreme pain in the left eye and the vision was disturbed. The

disturbance of vision gradually increased, becoming more intensive after every attack. In April, the visual field of the left eye was markedly narrowed, the upper and lower sphere being retracted.

Present Status. Temperature 36.8°C , pulse 70 to 80. No ptosis of eyelids. Paresis of left facial nerve. The corneal and conjunctival reflexes on left side abolished, and there is hypesthesia. Nystagmus present in both eyes. The left pupil indented and not circular and sluggish in light reflex. Vision: right 0.1, left 0.04. Both fundi show papillary congestion. Diminution of sense of touch and pain in the left half of face and mucous membrane. Olfactory sense lost in left. The sense of taste lost in the anterior two-thirds of the left half of tongue. The left ear-drum apparently normal but hearing disturbed. The bone conduction is extremely interrupted. Internal organs show nothing of note. The tendon and periosteal reflexes of extremities active, especially on left side. No Babinski's and Mendel-Bechterew's phenomena. Ataxia indefinite. Adiadochokinesis positive on the left hand. Wassermann test of serum negative. In spite of the negative Wassermann and possibilities of brain tumor, cerebrospinal syphilis was considered because of the extensive focal symptoms. Antiluetic treatment was given for a month without appreciable effects. In July the vision was invaded; amaurosis in the left eye, the right being capable only of counting fingers at close range. On June 15, cerebrospinal fluid was taken, which was xanthochromic and markedly positive in protein reaction. Spinal Wassermann negative. Accordingly the diagnosis of brain tumor is more probable.

A Case of Ischiatic Neuritis. CASE VIII.—Y. N., government official, aged forty-seven years.

Previous History. He did not remember having suffered from venereal diseases, but Wassermann test made eleven years ago was said to be positive. Ten years ago, had had sore throat and falling hair. In February, 1921, complained of tenderness along the right ischiatic nerve but in a month became a little better, due to medical treatment. At that time there was hypesthesia of the right toes. In October had a recurrence of the neuralgia, which in twenty days became very mild. In the middle of February of this year had dull pain along the left ischiatic nerve. In March this increased in intensity and extended down to the sole of the foot along the course of the ischiatic nerve.

Present Status. Pupils, vision, hearing, normal. Lymph-nodes not enlarged. Patellar and Achilles-tendon reflexes active. Slight tenderness of ischiatic nerves on pressure. Romberg's symptom positive. Gait slightly ataxic. There is hypesthesia in the median and posterior aspects of the left upper thigh. Wassermann test of serum markedly positive. On April 20, lumbar puncture performed.

A Case of Tuberculous Meningitis. CASE IX.—S. S., student, aged seventeen years.

Previous History. On February 9, 1922, had chill and fever. Had dry cough and headache with continuous high temperature. In March, felt as if oppressed on left breast. The patient showed symptoms of apical catarrh of right lung and pleuritis. From April 26, had attacks of headache and vomiting with diarrhea. In June, the headache subsided, nausea and vomiting still continuing. In the middle of June speech disturbance noted.

Present Status. On April 16, consciousness clouded and became lethargic. Pulse 90 per minute. Nystagmus present. Mydriasis in pupils. Lips dry, tongue coated. Movement of tongue disturbed. Marked stiff neck. Cervical glands enlarged to the size of a kidney bean. Thorax is flat and there is dulness in the right supraclavicular space over which respiratory sounds are weak. Pleuritic condition observed in the inferior and posterior parts of the right thorax, there being slight incurvature and rigidity of abdomen. Upper extremities show some resistance to the passive movements. Clonic movements of fingers. Fibrillary twitching marked in toes and calf. Knee and Achilles-tendon reflexes not particularly active. Kernig's phenomenon positive, Babinski's and Mendel-Bechterew's signs negative. On June 19 lumbar puncture performed. Patient died.

A Case of Epidemic Encephalitis with Kakké. CASE X.—K. G., farmer's wife, aged twenty-eight years.

Previous History. Spring of 1918, patient lapsed into lethargic condition without any noticeable cause. She complained of murmur in the left ear; had difficulty in hearing, double vision, and was light-shy. Does not know whether she had fever or not. In autumn paresis appeared in both sides of forearm and hands. Had had salivation for two years. Winter, 1921, paresis appeared in both feet. No venereal diseases.

Present Status. Countenance lethargic and appears as if smiling. No fever. No nystagmus. The right pupil is larger than the left. Pupils round, with absence of reflex to light. Heart-sounds impure in apex, second pulmonary sound is active and duplicated. The body posture attains that of Parkinson's disease, body bending forward. Gait and other movements sluggish. Limbs resist passive movements, there being rigidity in all muscles. Babinski positive in the right. Knee and Achilles-tendon reflexes are abolished. Paresthesia and hypesthesia present in both legs and the back of feet. Slight trace of albumin and urobilin in urine. June 24, lumbar puncture.

Result of Examinations. CASE I. Pressure 95 mm.; cells 4. Pandy negative; the first phase of Nonne-Apelt's test negative;

Wassermann reaction negative. The absorption curve (Chart I) shows a slight concavity under the wave length 2924° A in the thick layer and is almost horizontal between 2757° A and 2525° A. This means that there is no marked special absorption in this case.

CASE II.—Pressure 110 mm.; cells 6. Pandey, Wassermann, and the first phase of Nonne-Apelt's test negative. The absorption curve (Chart I) shows an end absorption in the thick layer, the base of the curve being horizontal between 2757° A and 2525° A.

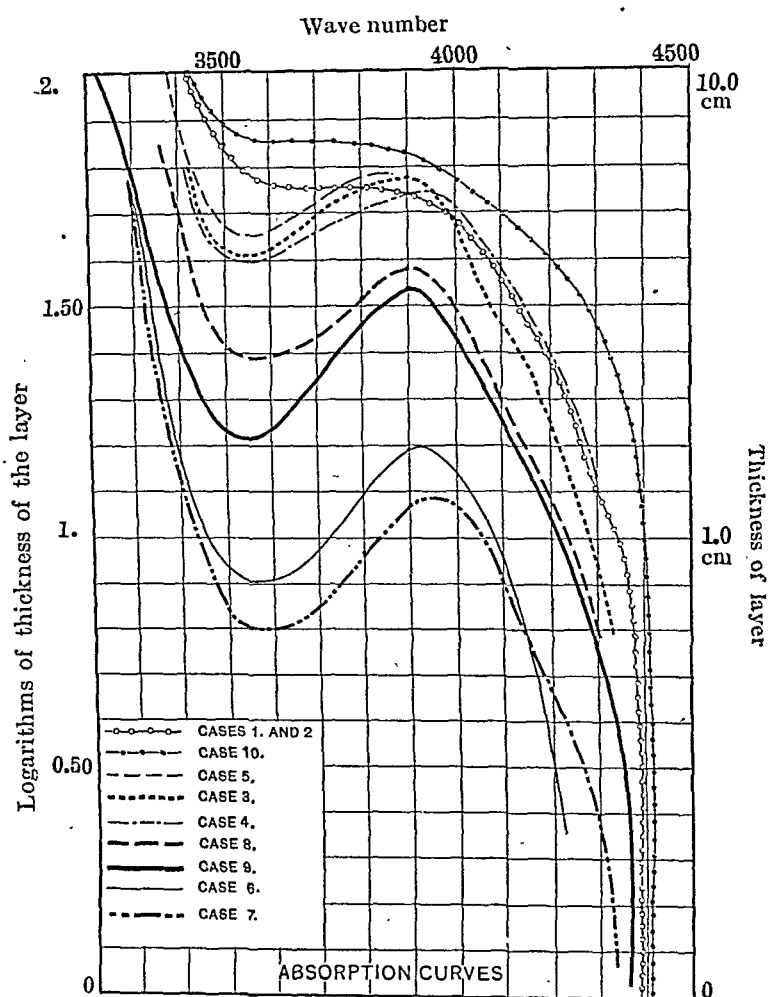


CHART I

These two cases are considered normal and the curves are almost the same. This type of curve is, therefore, designated as "normal curve."

CASE III.—Pressure 85; cells 6. Pandey and the first phase of Nonne-Apelt slightly positive; Wassermann test markedly positive. The special band absorption occurs between the wave length

2924° A and 2564° A, forming a decided valley. (Chart I.) The base of the valley falls in 4.0 cm. of the layer.

CASE IV.—Cells 28. Pandey and the first phase of Nonne-Apelt slightly positive; Wassermann negative. The absorption curve (Chart I) is similar to that of Case III, and a marked valley is shown between 2924° A and 2564° A, the bottom being in 4.0 cm. of the layer.

CASE V.—Pressure 120; cells 38. The first phase of Nonne-Apelt and Pandey slightly positive; Wassermann negative. The absorption curve (Chart I) duplicates those of Cases III and IV. The valley lies between 2924° A and 2564° A and the base in 4.5 cm. of the layer.

CASE VI.—The fluid is transparent but xanthochromic. Cells 8. The first phase of Nonne-Apelt, Pandey, and Wassermann all markedly positive. Hemoglobin negative by spectroscopical examination as well as in the spectrophotograph on panchromatic film. The valley of absorption curve (Chart I) is seen in the wave length between 2929° A and 2529° A and is so deep that the base of it reaches 0.8 cm. of the layer. This proves the existence of large amounts of absorbent substances.

CASE VII.—The fluid xanthochromic and transparent. Pressure 200. The first phase of Nonne-Apelt and Pandey strongly positive. Wassermann test negative. The valley of the absorption curve (Chart I) is the wave length between 2924° A and 2538° A, the base of it reaching 0.6 cm. of the layer.

CASE VIII.—Pressure 230; cells 12. First phase of Nonne-Apelt positive, Pandey markedly positive; Wassermann decidedly positive. The valley of the absorption curve (Chart I) is extremely deep, existing between the wave length 2924° A and 2564° A and the base is represented by 0.6 cm. of the layer. It is a well-known fact that the cerebrospinal fluid taken from patients suffering from ischiatic neuralgia contains more albumin than normal. In this case positive Wassermann and protein tests indicate a syphilitic process in the spinal meninges or in the nerve roots in addition to ischiatic neuritis.

CASE IX.—Pressure 440 mm.; cells 410, mostly lymphocytic with a few polynuclear leucocytes. Wassermann negative; Pandey and the first phase of Nonne-Apelt markedly positive. Cellular element removed by centrifuge and absorption spectra taken on supernatant fluid. The deep valley (Chart I) is formed between the wave length 2985° A and 2564° A and the basis in 1.6 cm. of the layer.

CASE X.—Pressure 120; cells 6. First phase of Nonne-Apelt, Pandy, and Wassermann reaction negative; Nylander's sugar test negative. The curve resembles the normal curve and the valley between 2857° A and 2632° A is nearly straight and lies in 7.0 cm. of the layer. (Chart I.)

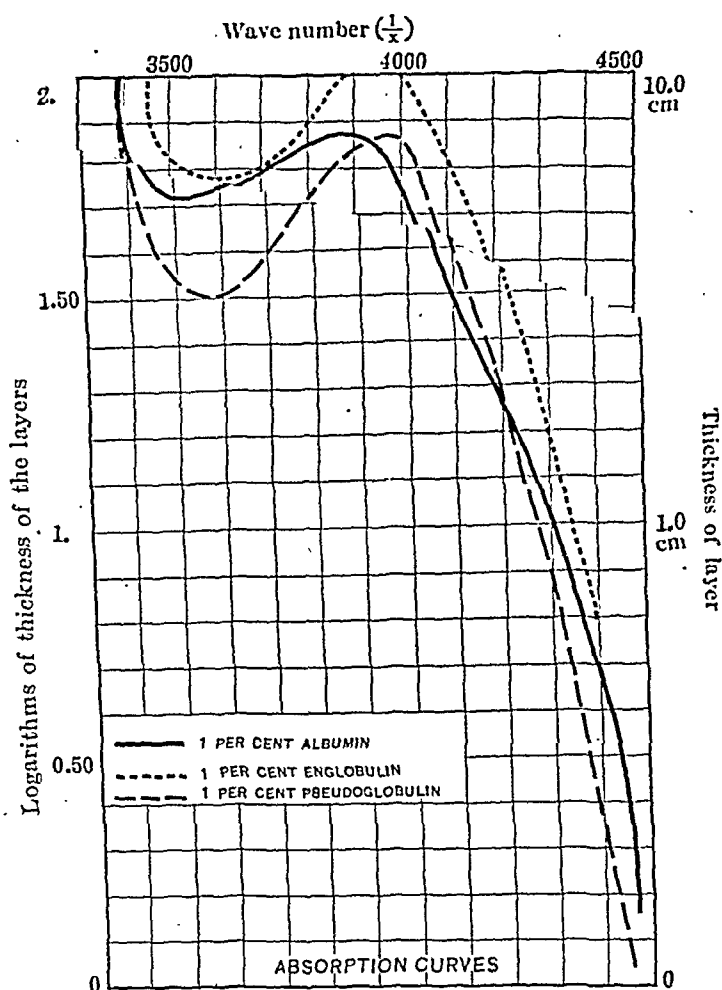


CHART II

Comment. From these results, it may be seen that the cerebrospinal fluid offers absorption on the spectrum of iron in the ultra-violet sphere nearly of the same wave length. The normal fluid presents a straight line, while abnormal fluids, except that of epidemic encephalitis, show a marked valley of absorption approximately between the wave length 2900° A and 2530° A. Although the thickness of layers which corresponds to the basis of valleys differs according to the density of the absorbing substances, the forms of the curves appear to be of the same type. The steepness of the curve, when compared with other tests of cerebrospinal fluid, does not correspond to that of the Wassermann test, but is parallel with that of protein tests, such as Nonne-Apelt and Pandy.

Thus it is presumable that the substance which gives rise to this curve is protein. What is the nature of the protein? Inorganic substances which absorb ultraviolet rays are complexes, and other colored salts and the simple salts have nothing to do with it. Organic substances have not been thoroughly studied in regard to this subject, although a little has been done on some proteins, uric acid, glucose, and dyes.^{3 4 5} Urea does not show absorption by my own study. Soret and Hartley found absorption of glucose between 2220° A and 2150° A of the wave length respectively, while in my case it was shown in the wave length between 2900° A and 2530° A. Soret gives the absorption of globulin in the wave length 2900° A, of albumin in 2740° A; Hartley, of albumin between 2948° A and 2572° A, while Blyth claims that all protein substances would show absorption in nearly the same wave length.⁶

Recently (March, 1922) Lewis⁷ has reported that three kinds of serum protein are practically the same with respect to the absorption curve. The writer has studied the absorption of ultraviolet rays on albumin, euglobulin, and pseudoglobulin of horse serum, not having the report of the above worker at that time. Using 0.1 per cent of the solution, albumin has shown absorption in the wave lengths between 2941° A and 2584° A (basis 5.3 cm.), euglobulin between 2924° A and 2551° A (basis 6.0 cm.), and pseudoglobulin between 2941° A and 2538° A (basis 3.2 cm.). The absorption curves of these three proteins (Chart II) are much alike and are in remarkable accordance with the results of the last-named worker. The substances in the pathological fluid which have the property of absorbing ultraviolet rays are most probably protein bodies. But as to the exact nature of the protein the present study offers nothing very definite.

Conclusions. The author studied the absorption spectra of the cerebrospinal fluids taken from patients suffering from several kinds of diseases of the cerebrospinal system and plotted the absorption curves to compare it with that of normal fluid.

In the normal fluid the curve was shown with slight concavity between the wave lengths 2924° A and 2525° A in the thick layer, and was almost horizontal between 2757° A and 2525° A. This means that there is no special absorption band; this was designated as the "normal curve." The pathological specimen, except that of the epidemic encephalitis, manifested marked concavity in the same wave lengths (between 2924° A and 2520° A), the depth of the valley varying with the different diseases. The formation of the valley and its depth were proportional to the degree of the protein tests (Nonne-Apelt, Pandy) but not to the Wassermann reaction. The curve of epidemic encephalitis was practically the same as normal.

The serum albumin, euglobulin, and pseudoglobulin would show absorption in nearly the same wave lengths and the forms of their

curves and locations are in accordance with the pathological fluid. Therefore it may be presumed that the absorption spectra in the ultraviolet rays is due to protein. According to the depth of the valley, the concentration of protein can be roughly estimated. But as for the nature of the protein this study gives no definite information. The test can be applied together with the known tests for diagnostic purposes. It is more scientific than the usual tests which depend upon the intensity of cloudiness, insofar as this test expresses the quantity in the numerical manner. Another advantage lies in the fact that the fluid used for this can be subjected to other examinations without any change in either the quantity or quality of the fluid.

The writer is greatly indebted to the instruction of Dr. K. Miura, professor of internal medicine, Imperial University of Tokio, and to the valuable coöperation of Dr. Y. Shibata, professor of science, and his assistant, Dr. T. Inouye in completing this report. To these he wishes to express his deepest gratitude.

BIBLIOGRAPHY.

1. Beer, A.: Bestimmung der Absorption des roten Lichtes im farbigen Flüssigkeiten, Pogg. Ann., 1852, p. 86.
2. Hartley, W. N.: Researches on Spectrum Photography in Relation to New Method of Quantitative Chemical Analysis, Philadelphia Trans. 175, 1884, 1, 49.
3. Soret: Kaysers Handbuch der Spectroskopie, vol. 4.
4. Hartley, W. N.: Spectroscopic Notes on the Carbohydrates and Albuminoids from Grain, Trans. Chem. Soc., 1887, 51, 58.
5. Blyth, W.: Ultraviolet Absorption Spectrum of Proteid in Relation to Tyrosine, Trans. Chem. Soc., 1899, 75, 1162.
6. Soret, Hartley and Blyth: Loc. cit.
7. Lewis, J.: Ultraviolet Absorption Spectra and the Optical Rotation of the Proteins of Blood Sera, Proc. of the Royal Soc., Series B., 1922, 93, 178.

REVIEWS.

LOCAL ANESTHESIA: ITS SCIENTIFIC BASES AND PRACTICAL USE.

By PROF. DR. HENRICH BRAUN, Obermedizinalrat and Director of Kgl. Hospital at Zwickau, Germany. Translated and Edited by MALCOLM L. HARRIS, M.D., Professor of Surgery, Chicago Polyclinic; Chief Surgeon, Alexian Brothers Hospital; Surgeon to the Henrotin, Polyclinic and Passavant Hospitals, Chicago, Ill. Second American from the Sixth German (revised) Edition. Pp. 411; 231 illustrations. Philadelphia: Lea & Febiger, 1924.

THE first American translation from the third revised German edition in 1914, was one of the earliest works on local anesthesia to group and standardize these measures as we know them today. The present volume comprises the material of the former thoroughly revised with the addition of the newer ideas bringing it up to the present date. Various comments, throughout, are made by the American Editor. To Braun we owe the addition of adrenalin to our anesthetic equipment, this subject is therefore well worthy of our close study; it is presented in a style simple but masterly. Of interest among the additions is a toxic standard for novocain, a method of locating the various subcutaneous and deeper nerves before injection; a discourse on lumbar (spinal) anesthesia and sacral routes. Spinal anesthesia is treated in a manner which will undoubtedly give satisfaction in the majority of cases, but admits of one technic and, at most, two drugs. The percentage of failures is rather high according to our American standards, and in arriving at these figures no mention is made of the drug used, it is to be supposed that the ones mentioned in the text are the ones used. Chapter X on the advantages of local anesthesia and its particular uses make very helpful reading. A new route for injection of the trigeminal nerve is well written. Chapter XII, dealing with the neck, is entirely rewritten, while particular mention is made of the injection for operations on the thyroid and larynx. A graphic chart of the innervation of the thorax and its block anesthetic possibilities make of this subject a broad field of endeavor. Abdominal operative technic of local anesthesia are revised and thoroughly explained. Parasacral anesthesia is given a rightly important position and numerous heretofore difficult operative procedures under local are

made easily within the realm of the careful surgeon. A discussion of plexus anesthesia and its dangers to be avoided is handled well and methodically. The print in this edition is smaller and placed more close but the reading is easy and interesting. It is bound well and attractively.

W.

MODERN UROLOGY. In Original Contributions by American Authors. Edited by HUGH CABOT, M.D., C.M.G., F.A.C.S., Dean and Professor of Surgery, Medical School, University of Michigan. Second edition. Two volumes. Pp. 1516; 686 illustrations and 19 colored plates. Philadelphia: Lea & Febiger, 1924.

ONE welcomes the appearance of a second edition of this most excellent and valuable work, representative of the best in American urology. Much has been accomplished in improving the first edition's mistakes and reduplications.

In Volume I is missed the interesting historical chapter by Watson, now deleted. The chapter on roentgenology is rewritten and with better illustrations. Corbus on syphilis now includes the subjects of luetic cystitis and the tabetic bladder; his chapter on genital ulcers presents the recent work on granulomas. Fowler includes Churchman's new operation for hypospadias and Young's for epispadias, while Ballinger has added a good word for acriflavine to his treatment of gonorrhea. Barney completely rewrites his splendid exposition of tuberculosis, and Hinman writes anew the chapter on testicular tumors as an authority that none question. Gardner also appears as a new collaborator and vastly improves the chapter on prostatic obstructions. On page 100, 4 per cent indigo-carmin solution is advised where a 0.4 per cent solution is certainly meant and was correct in the first edition.

Volume II on the whole shows less change. Peculiarly, Lower does not refer to Cullen's book on the umbilicus in dealing with vesical malformations; it would broaden his presentation. He rewrites the subject of diverticulum and presents his valuable work on exstrophy. Caulk includes just enough on Hunner's ulcers. Geraghty keeps apace with the times on the all-important subject of bladder neoplasms, and is now able to present some of his results with modern methods of treatment and the conclusions to be drawn therefrom; as may be likewise said of Young's chapter on prostatic carcinoma. The contributions of Keyes and of Cabot show very minor changes and the reviewer feels that many will agree with him that it is to be regretted that there is not more in the two volumes from the pens of these two most readable authors. The books appear in excellent sized volumes, handsomely edited.

R.

INTRA-NASAL SURGERY. By J. A. PRATT, M.D. Pp. 334; 195 illustrations. Philadelphia: F. A. Davis Company, 1924.

ONE is immediately impressed in reviewing this work with the clearness of text and the profusion of illustration. It first reviews the fundamental anatomy, physiology and pathology of the nasal cavity, and then includes among much miscellaneous material, special chapters on Atrophic Rhinitis, Submucous Septal Surgery, Development of the Lateral Wall, Turbinates, Ethmoidal Cells and Various Sinuses.

Nearly twenty full roentgen-ray plates are included in the book, with many working instruments *in situ* which concludes with a dozen coronal sections of the head, arranged in series. It is replete with suggestive points from practical experience, scarcely needed by the trained specialist; for him a more comprehensive description of the various sinus operations might be included.

While occasionally one might not entirely agree with the author's selective viewpoint, this work is however, a last word in the illustration of operative technic and a real contribution to literature.

B.

PRACTICAL CHEMICAL ANALYSIS OF BLOOD. By VICTOR CARYL MYERS, M.A., PH.D., Professor and Director of the Department of Biochemistry, New York Post-Graduate Medical School and Hospital. Second revised edition. Pp. 232; 33 illustrations. St. Louis: C. V. Mosby Company, 1924.

THIS new edition brings entirely up to date the subjects so well presented in the first edition. All the important blood determinations are here described carefully and in detail for the guidance of the laboratory worker. The significance and interpretation of these tests are properly evaluated for the clinician. There are also chapters on micromethods of urine analysis, on colorimeters, on standard solutions and reagents, and at the end of each chapter is an excellent bibliography.

F-H.

INTRAVENOUS THERAPY. By WALTON FOREST DUTTON, M.D., Medical Director, Polyclinic and Medico-Chirurgical Hospitals; Graduate School of Medicine, University of Pennsylvania. Pp. 542; 59 illustrations. Philadelphia: F. A. Davis Company, 1924.

THE first half of this book deals with the "General Technic of Intravenous Therapy" which is well presented. Unnecessary space

is devoted to certain matters, however, such as direct "artery to vein" transfusion. The second part of the book is a sort of medical compendium containing a list of apparently every disease for which anyone has ever recommended any form of intravenous medication. In each instance in addition to the suggestions for intravenous treatment is given an unnecessary "rehash" of the usual text-book symptoms, diagnostic points, and general methods of treatment. There is also an appendix containing tables of dosage, weights and measures, and tables of equivalents. F-H.

PEDIATRICS. By VARIOUS AUTHORS. Edited by ISAAC A. ABT, M.D., Professor of Diseases of Children. Northwestern University Medical School. In eight volumes. Volume I; 1240 pp. 284 illustrations. Volume II; 1025 pp.; 180 illustrations. Philadelphia: W. B. Saunders Company, 1923.

ENGLISH pediatric literature is rich in modern text-books and monographs, but no such comprehensive compilation as Abt's System has been published since Keating's "Encyclopedia" and "Supplement." In the quarter of a century intervening, the number of American and British investigators has been enormously increased and a vast amount of new knowledge has been acquired. A modern encyclopedia on children should be an inspiration to students, an aid to investigators, a boon to practitioners, and should be an incentive to a more scientific study of children in health and disease. Abt's Pediatrics will meet these needs. Most of the articles with their good bibliographies, are comprehensive enough to be of great value as works of reference; but in addition, the practical features are so clearly, logically and prominently presented, that they will appeal to the wearied practitioner.

The volumes consist of collections of monographs by a well-chosen list of authors. Although the Great War, and conditions following, delayed the publication of the work, most of the sections have been successfully revised or rewritten.

The first book contains a Survey of Encyclopedic Literature by Dr. Abt, a History of Pediatrics by Fielding H. Garrison, Congenital and Acquired Predisposition and Heredity by Clarence C. Little, a Summary of Anatomy by Richard E. Scammon, Growth and Development by T. Brailsford Robertson, Physiology of Metabolism by John R. Murlin, Application of Physical Chemistry to the Physiology of Childhood by Jesse F. McClendon, Hygiene of the School Age by Josephine E. Young, Hygiene of the Home, and Hygiene of Infants by Walter R. Ramsay, Climatotherapy by F. L. Wakeham, and Hygiene of Crippled Children by H. Winnett Orr.

Garrison's article is a fascinating and valuable résumé of facts

which, from primitive times, have had bearing on the development of the practice of pediatrics.

Of great scientific importance is the rather technical paper by Little. The statement that: "permanent racial improvement will come insofar as the germ plasma is improved, and no farther" may seem discouraging to many who are earnestly endeavoring to uplift the race by improving social and environmental conditions. The author, however, approves of such efforts, as they contribute to physical and mental progress, though they cannot alter the germ, but he would extend and amplify them. He makes a definite appeal to the medical profession to consider most seriously the question of human genetics in its relation to childhood and to racial development.

In the chapter on the anatomy of infants and children, much data from many sources is collected. The subject is of such importance, and is so well handled by Dr. Scammon, that more than 171 pages might advantageously have been given it. However, the superb bibliography chosen from about 5000 papers covers the subject completely.

Dr. Robertson throws new light on the question of growth and development, which will be of particular value to those interested in anthropometry. All persons responsible for the proper physical development of children should read this classic article.

The chapter on metabolism is most valuable. Dr. Murlin considers the metabolism of the newborn, the infant, and the child very completely under the title of Energy Metabolism. Under Substance Metabolism he goes into detail concerning the digestion, the absorption, and the intermediary metabolism of proteins and salts as they occur in the child. Discussion of the metabolism of fats and of carbohydrates is very brief, apparently due to the fact that protein and salts, constitute the "substrata of living protoplasm" and therefore concern metabolism most specifically. The bibliography covers the literature very well up to 1920 and contains some references as late as 1922.

The short lucid chapter on The Application of Physical Chemistry to the Physiology of Childhood will be greatly appreciated by many whose academic instruction in chemistry did not include electric conductivity, thermodynamics, hydrogen-ion concentration, etc.

Dr. Young has written an exhaustive article on the hygiene of the school child, that all physicians and school administrators should read. Every phase of child hygiene is considered fully; and much practical information is offered concerning posture, speech defects, exercise, sex hygiene and mental hygiene. School-health administration is also discussed at length.

The other chapters in Volume I are not sufficiently comprehensive for a reference book.

The second volume is comprised of sections on: Mortalities by

Richard Arthur Bolt, History-Taking Physical Examination by Mark Jampolis, Cerebrospinal Fluid, by Abraham Levinson, Roentgenology by Frederick C. Rodda, Peculiarities of Disease in Childhood by John Diven, Prophylaxis and Treatment by L. R. DeBuys, Heliotherapy by Henry Dietrich, Diseases of the Newborn by N. O. Pearce, Premature Infants by Julius H. Hess, Chemistry and Biology of Milk by Paul G. Heineman, Breast Feeding and Nutrition by Julius P. Sedgwick and Wyman G. C. Cole, Artificial Feeding of Infants by Joseph Brennemann, Diabetes Mellitus by Solomon Strouse, Diabetes Insipidus by Max Kahn, Seasickness by William J. Corcoran, Beriberi by Edward B. Vedder, Acidosis by John Howland and W. McKim Marriott, Obesity by T. C. Hempelmann, Infantile Scurvy (Barlow's Disease) by Alfred F. Hess, Pellagra by J. Ross Snyder, Rickets by Alfred F. Hess, The Constitutional Diathesis of Childhood by Frederic W. Schultz, and Aerodynia by William Weston.

Dr. Bolt's contribution is not an uninteresting statistical report on infant mortality, but an entertaining and instructive presentation of facts which prove the statement that "infant mortality can and should be largely prevented." The direct and contributing causes of infant mortality are discussed in a comprehensive manner, yet so clearly, that the reader wonders at the simplicity of the problem of prophylaxis, even though he appreciates the multiplicity of predisposing causes of disease. The author would solve the problem by education of the profession in medico-social pediatrics and in child-welfare work.

A chapter on Cerebrospinal Fluid summarizes the important facts concerning this fluid in a satisfactory and very convenient way. The editor and the author are to be congratulated for devoting a chapter to this subject.

Dr. Frederick C. Rodda discusses Roentgenology in reference to diseases of the lungs, pleura and mediastinum. So well is this phase of the subject presented, and so excellent are the illustrations, that one regrets the author did not also consider roentgenology in its relation to abnormalities of the gastro-intestinal tract and to bone diseases. However, these phases of the subject will probably be fully discussed later with the individual diseases. In fact, the finished articles on rickets and on scurvy in this volume, justify such expectation.

The section on Peculiarities of Disease in Childhood is especially valuable to those practitioners, who, not having made a special study of children, usually attempt to interpret the physical signs in infants and young children by comparison with normal standards for adults. Observation of the examination technic of the average hospital intern or of many general practitioners furnishes sufficient justification for such a chapter. Were Dr. Diven's article subdivided under various headings, its information would be more readily accessible.

The 83-page section on Prophylaxis and Treatment is chiefly a summary of methods of treatment. General treatment, care and nursing, aerotherapy, climatotherapy, dietotherapy, psychotherapy, therapeutic technic, hydrotherapy, electrotherapy, roentgen- and radiotherapy, and serum, vaccine and drug therapy are dealt with in 80 pages, including 25 pages which are devoted to a practical table of drugs and of dosage. Surely "prophylaxis" deserves more detailed consideration in an encyclopedia. Presumably the abridgment under this heading was due to a desire to avoid repetition, for several chapters in the preceding volume are devoted to various phases of prophylaxis. The chapter on Heliotherapy by Henry Dietrich is an interesting complement to DeBuy's treatise, but is not sufficiently comprehensive.

Two of the most noteworthy articles of this volume are Diseases of the Newborn by Dr. N. O. Pearce, and Premature Infants by Dr. Julius Hess. Both are so complete and practical that every physician interested in pediatrics, obstetrics, or public health, should read them.

Many practical points are found in the chapter on the chemistry and biology of milk. Following this, is the paper on breast feeding which summarizes the fundamental facts which every practitioner should have at hand.

The section on Artificial Feeding of Infants is a thorough, clear, simple, delightfully written exposition of the science and of the art of artificial feeding. It should do much toward removing the unfortunate and unwarranted mysticism that seems to surround the subject. Dr. Brennemann sanely appeals to the practitioner to master the few fundamental scientific facts concerning digestion, nutrition, elimination, etc., and to "know very definitely the behavior in the infantile economy of the different food elements, and the effect of modifying them so as to influence that behavior." This knowledge he truly claims may be acquired by "any intelligent graduate of medicine in a comparatively short time." He then urges the doctor to carefully and conscientiously study the baby and its environment and to apply his knowledge to the individual. The food should be adapted to the baby's needs, not to a prearranged table, not to meet a theory or "system." Perhaps few pediatricists will endorse all of Dr. Brennemann's conclusions and opinions, but his effort to bring the subject of infant feeding within the easy grasp of the family physician should meet with universal acclaim. For it is only through education of the doctor that the art of feeding will revert to him from the patent-food manufacturer.

The latter part of Volume II deals with definite diseases of children, all of which are very ably handled. It is surprising that in the discussion of diabetes only two paragraphs are given to the insulin treatment. Doctors Howland and Marriott have made a distinct contribution in their clear, concise discussion of acidosis.

Dr. Alfred Hess brings the subjects of scurvy and rickets up to date in two masterly monographs. The article on Pellagra is excellent, though it contains no reference to observations since 1917. The chapter on The Constitutional Diatheses of Childhood well repays careful perusal.

If the succeeding volumes are commensurate with these first two, Dr. Abt will creditably succeed in collecting "in monographic form the material which represents the fundamental knowledge of pediatrics" and will most probably attain his aspiration "to stimulate clinical and research work, especially by the younger men of English speaking countries." The compilation is so excellent that one regrets it has not been published in the loose-leaf form, so that revisions and additions might be readily made at short intervals of time. F.

FORTY-THREE GRAFTS FROM MONKEY TO MAN. BY SERGE VORONOFF. Pp. 256; 38 illustrations. Paris: Doin, 1924.

THE author first gives the names of the surgeons who have used his method of grafting and then those who have assisted him in the operation. The list is too extensive to review. He gives as the indications for the operations the following: Absence of the testicle from castration, infantilism of the genital organs, orchitis following mumps, myopathies, chronic intoxications resulting in general asthenia, insufficiency of testicular secretion, neuresthenia, arteriosclerosis with premature senility, and senility with general debility. The results as given by the author are: Mortality, none, negative results, five (12 per cent). The latter were due to the use of an orchid from too young a chimpanzee. The positive results from the point of view of mental and physical improvement are given as 88 per cent (36 cases). Results from the point of view of mental, physical and sexual virility 65 per cent (26 cases). The age of the patients varied from twenty to seventy-six years.

The chimpanzee and cynocephale monkey being the nearest relations of the man were the only donors used. A graft made between two markedly distinct species undergoes necrosis rapidly. Minute researches as to the age of the "donor" have led to the conclusion that the monkey must have reached puberty or must be very near it.

The result of it all is indisputably favorable according to the author. Sexual power has, in many cases, not been restored which, according to the author, is a very small matter. The regaining of memory, the power to be able to "think and not feel tired," the general "young again" feeling were the main results which have encouraged the author in his work.

Although the author ascribes very little to the power of auto

suggestion, the reviewer believes this to be an important factor. Some of the illustrations appear to be convincing, but many are taken with varying backgrounds and intensities of the exposures. From the latter point of view, the reviewer feels that the pictures are inadequate and not convincing. Sixteen of his cases had gland transplantation for arteriosclerosis with general debility. It seems impossible to imagine an atheromatous vessel undergoing resolution and again taking on the characteristics of a normal one. It is but natural that the results seem more favorable to the expounder of the idea than to an unprejudiced critic. R.

WALTER REED AND YELLOW FEVER. By HOWARD A. KELLY, M.D. Third edition. Pp. 355; 15 illustrations. Baltimore: The Norman, Remington Company, 1923.

THE new edition has had certain minor additions made which have added but little to the value or interest of the book. The chapters which concern Walter Reed and his work are of intense interest but the added chapters concerning General Sternberg and General Gorgas, while perhaps rounding out the story do not seem as interesting or as well written. P.

EXCURSIONS INTO SURGICAL SUBJECTS. By JOHN B. DEEVER, M.D., ScD., LL.D., F.A.C.S., Emeritus Professor of Surgery; and STANLEY P. REIMANN, M.D., Assistant Professor of Experimental Pathology, University of Pennsylvania. Pp. 188; 30 illustrations. Philadelphia and London: W. B. Saunders Company, 1923:

THE volume comprises a group of lectures delivered by the senior author in July, 1922, at Washington University, Seattle, Wash., in the Extension Course for Graduate Physicians, also Dr. Deaver's address on the Centenary of Pasteur, an essay on Medical Education and Educators and a previously published paper on Living Pathology.

The lectures embrace peptic ulcer, jaundice, diseases of the bile passages and surgical conditions of the intestinal tract. The authoritative clinical views, based upon exceptionally rich experience, and the discussions of pathology, research and results of treatment, collaborating the work of an eminent surgeon and teacher with that of a brilliant pathologist and illustrating the invaluable coöperation between the amphitheatre and laboratory, make the kind of surgical literature that meets the requirements of the leaders of the profession as well as their progressive followers. L.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI,
CINCINNATI, OHIO.

The Staining of *Treponema Pallidum* in Dry Smears.—RUTH GILBERT and H. A. BARTELS (*Jour. Lab. and Clin. Med.*, 1924, 60, 273) have prepared smears from the testicles of syphilitic rabbits. The presence of spirochetes has been demonstrated by dark-field illumination. The smears were divided into two sets, one of which was fixed immediately by heat, the other after an interval of four days (taking into consideration the time lost in transportation of specimens to a laboratory). The specimens were then stained and examined. The following staining methods were tried, 25 smears being stained by each method: Fontana, Tribondeau, Becker, Noguchi, Rosenberger and Fanz, Lipp, Ballenger, Medallia, Proca and Vasilescu, Oppenheim and Sachs, Reitman and Benian. One hundred and fifteen of the 375 smears examined were found positive. The following percentages of positives were found after staining with each of these methods: Fontana's method 80 per cent; Becker's method 60 per cent; Rosenberger and Fanz 28 per cent; and Lipp's method 24 per cent. The remaining methods were found to be useless. Seventy-five additional smears stained by Fontana's method gave 59 per cent positives. The morphology of *Treponema pallidum* in smears fixed after an interval of four days did not differ from that in smears fixed immediately. The technic used in Fontana's method was as follows: 1. Smears were air-dried and fixed with Hüge's fluid (glacial acetic acid 1 cc; formalin 20 cc; and distilled water 100 cc) for one minute. 2. They were next washed in water, then covered with mordant of 5 per cent tannic acid, in 1 per cent carbolic acid solution, and heated until steam arose. The heated mordant was allowed to act thirty seconds. 3. Smears were rinsed quickly in water, blotted, and covered with a 2 per cent ammoniacal silver nitrate solution. (Ammonia should be added drop by drop

to the silver nitrate solution until a faint opalescence succeeds the brown precipitate first produced.) Heat was applied until steam arose and the heated stain was allowed to act thirty seconds. 4. The specimens were finally washed, blotted and examined.

Treatment of Myeloid Leukemia with Thorium X.—CH. AUBERTIN (*Bull. et mém. Soc. méd. d. hôp., Paris*, 1924, 40, 4) observed a considerable leukopenia (to 1500) in patients with chronic arthritis treated with thorium X; there was a modification of the leukocytic formula, consisting in polynucleosis and eosinophilia. These changes persisted during the course of the injections. There was no noteworthy change in the red count; nor was there any constitutional disturbance. In view of these facts, the author decided to try thorium X in the treatment of leukemia. A number of reports of its use in leukemia occurred during 1912-14, but since then, it seems to have been abandoned. The patient, a man aged fifty-five years, had been ill two months. He had a marked splenomegaly. Blood examination showed 2,850,000 red cells and 22,500 leukocytes, with 30 per cent myelocytes. Treatment was begun March 13, 1923 with subcutaneous injections of 300 micrograms; seven such injections were given at intervals of a week, then 400 micrograms and 200 micrograms were given. There was no local reaction, but each time the patient complained that they became painful. (He was an ambulatory patient, coming for the injection each week.) The treatments were discontinued May 16, the leukocyte count having fallen to 2700. Between June 29 and August 6 he had three roentgen-ray treatments. In August, all treatment was discontinued; leukocytes 1500, erythrocytes 1,460,00. The spleen was much decreased in size. November 25, the leukocyte count was still low, 3300. The red count, which had fallen to 1,670,000 June 16, rose to 2,870,000 in November.

Differential counts showed the following:

	Mar. 13, 1923, before treatment.	June 14, 1923, end of treatment.	Oct. 18, 1923, without treatment.
White count	22,500	2700	1500
Polynuclear neutrophiles	50.75%	64.0%	68.5%
Myelocytic neutrophiles	29.75%	13.0%	5.5%
Polymorphonuclear eosinophiles . .	2.00%	0.5%	2.0%
Myelocytic eosinophiles	1.25%	0.5%	2.0%
Polymorphonuclear basophiles . .	1.25%	0.5%	2.5%
Myelocytic basophiles	1.25%	0.5%	2.5%
Myeloblasts	1.50%	3.7%	5.0%
Lymphocytes	7.25%	14.0%	15.5%
Large mononuclears	6.25%	4.5%	6.5%
Normoblasts	1 to 400	3 to 200	3 to 200
Megaloblasts	2 to 400	3 to 200	3 to 200

The spleen showed little change in size during the course of the treatment, but later there was a steady decrease in size, which began sometime after treatment was discontinued.

An Analysis of the Clinical Histories of Patients with Pernicious Anemia in the Johns Hopkins Hospital from 1918 to 1922 Inclusive—C. R. WILLSON and F. R. EVANS (*Bull. Johns Hopkins Hosp.*, 1924, 35, 38) have analyzed the histories of 111 cases of pernicious anemia

and emphasize the following points: Pernicious anemia is about equally common in men and women and is a disease of adult life. It is never seen in children, is common in old age, and occurs most frequently between the ages of forty and sixty. It is very uncommon in negroes. The anemia once established, practically never regenerates. Anisocytosis and poikilocytosis are constant findings. Although a leukocytosis may occur in the presence of an infection, a leukopenia is the characteristic finding. An eosinophilia as high as 17 per cent may be found, but the increase is usually relative. The same applies to the large mononuclear and transitional cells. Myelocytes as high as 10 per cent may be found in an occasional case. Free hydrochloric acid in the gastric contents of these patients is so rare that, when present, it should put the diagnosis under suspicion. The spleen is palpable in only about 20 per cent of the patients. It may extend 5 or 6 cm. below the costal margin. The liver is palpable in about 33 per cent of cases. The edge may be palpated 5 or 6 cm. below the costal margin. All patients, whatever other discomforts they may have, suffer from one or more of the following symptoms: Weakness, disturbances of digestion, and nervous disorders of the extremities.

On the Phosphorus and Calcium of the Blood in Renal Disease.—

O. L. V. DE WESSELOW (*Quart. Jour. Med.*, 1923, 16, 341) reports a study of the phosphorus and calcium content of the blood in kidney disease and arrives at the following conclusions: A marked increase of the phosphate content of the blood in nephritis is of extremely grave import. The symptoms of uremia appear to show a close relationship to phosphate retention. On the average, retentions of phosphate and urea run a parallel course; the excretory mechanism of the two bodies is therefore probably the same. Independent variations in the retention of the two bodies are frequently observed, and are probably due to circumstances extraneous to the renal function. A diminished content of serum calcium is a bad omen, and appears to be connected with the generalized tremor and local twitchings of the final stages of uremia. No connection has been found between a diminution in the serum calcium and the generalized convulsions. The calcium-content of the serum in nephritis appears to show an inverse relationship to the content of inorganic phosphorus.

Bacteriological Observations on Acute Tonsillitis with Reference to Epidemiology and Susceptibility.—BLOOMFIELD and FELTY (*Arch. Int. Med.*, 1923, 32, 483) used as material for their observations a group of about 200 young women, whom they were able to control as regards cultures, contact, etc. All cases of acute follicular tonsillitis were found to be due to hemolytic streptococci of the beta type. The organism may persist indefinitely in the tonsil, but rapidly dies out on the free mucous membranes. Carriers almost universally failed to develop the infection. There was an absence of demonstrable contact between successive or coincident cases. Evidence is adduced to show that the outbreak studied consisted of multiple instances of sporadic infection. There was a much higher incidence of the disease among individuals still possessing their tonsils. Of 104 persons with tonsils remaining,

41 were carriers of beta hemolytic streptococci, 63 were non-carriers. One individual of the 41 developed tonsillitis; 26 of the 63 developed the infection. Of the non-tonsillectomized, non-carriers who developed tonsillitis, a large proportion gave a history of previous tonsillitis. Their observations indicate that if a person reaches twenty years without having had tonsillitis, he has relatively slight chance of acquiring the infection.

Gonorrheal Myelitis.—PHIFER and FORSTER (*Arch. Int. Med.*, 1923, 32, 530) point out the rarity of myelitis due to the gonococcus and give a bibliography of the 29 reported cases. The authors add 2 instances. One individual developed myelitis in the course of an acute gonorrhea, the other in a chronic urethritis. In most of the reported cases, the gonorrhea was said to be chronic. One patient died; 1 recovered completely. Of the cases on record, there was a death-rate of about 25 per cent. The endocardium is relatively seldom involved. The symptoms are those common to a myelitis from any cause. In neither of the authors' cases was the gonococcus recovered from the spinal fluid, but the etiological responsibility of this organism seems to be fairly clear.

Two Cases of Canine Tuberculosis Caused by Human Tubercle Bacilli.—PANISSET and VERGE (*Compt. rend. Soc. de biol.*, 1924, 90, 341) investigated the origin of the tubercle bacilli in two dogs suffering with pulmonary tuberculosis with cavitation and rather marked hypertrophic osteo-arthritis. They inoculated Petroff's medium with pus from the cavities according to the method of Limousin (*Ann. de l'Inst. Pasteur*, 1921, p. 558). Direct smears of the pus contained numerous acid-fast bacilli. After three weeks' incubation, several tubes gave a pure culture of tubercle bacilli. Several colonies were removed and dried between sterile filter papers; $\frac{1}{100}$ mg. of bacilli were injected into the ear vein of young rabbits, according to the method of Park and Krumwiede. Autopsies six months later showed a disseminated tuberculosis in 3 of 4 animals. The tubercles were found in the lungs, kidneys and a few in the liver, and were in various stages of evolution; they contained tubercle bacilli. These observations indicate the danger to human beings from contact with tuberculous dogs.

Local Vaccination of the Intestine Against Dysentery.—ANGLADE (*Compt. rend. Soc. de biol.*, 1924, 90, 395) encountered an epidemic of bacillary dysentery in July, 1923, in the Garrison of Versailles, affecting chiefly the troops of Camp de Satory. There were also many cases among civilians. The first 3 cases were rapidly fatal, death ensuing in three to four days. An attempt at antidysenteric vaccination by means of oral administration, using the procedure of Besredka, was decided upon. There were 1132 soldiers in the camp. Of these 546 were vaccinated and 42 or 7.6 per cent developed dysentery; 586 were not vaccinated and 235 or 40 per cent of them contracted dysentery. Among the vaccinated it was learned that several retained the tablets in the mouth and expectorated them later.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Treatment of Hypertrophic Pyloric Stenosis.—POYNTON and HIGGINS (*Lancet*, 1924, 206, 235) declare that the essential step in successful result is the surgical procedure. When once the diagnosis has been made operate at the earliest opportunity. Tumors were in all cases felt. Their method of examination was described in full. The difficult tumors are those lying high up under the edge of the liver, but they can usually be detected on inspiration by their harder consistence. The great hindrance to a successful result has been the duration of the symptoms. A strong infant with a long history of starvation is more likely to succumb than a weakly one with a recent history. Preoperative treatment and operation, which consists in division of sphincter, with refinements in controlling hemorrhage, are described.

Surgical Treatment of Unilateral Pulmonary Tuberculosis.—ARCHIBOLD (*Am. Jour. Surg.*, 1924, 37, 17) states that the evidence of resistance is the prime essential and in this particular the help of the expert in tuberculosis is necessary. Fever, rapid pulse, large amounts of sputum and numerous bacilli are not contraindications. The author feels that it is best to do a thoracoplasty at the start, especially in those in whom it is going to be difficult to secure regular refills for pneumothorax, which he was formerly accustomed to do routinely. He describes his technic and after-treatment in full. In only 1 case out of 37 has the author experienced an acute invasion of the sound lung, presumably from operation. Postoperative shock has been conspicuous by its absence. The two-stage operation has become routine. One death in 39 thoracoplasties was directly due to operation—cardiac failure on the twelfth day.

Carcinoma of the Colon.—ROMANIS (*Brit. Med. Jour.*, 1924, 183, 3292) says the disease is both common and insidious. Early diagnosis is admittedly difficult. Uncomfortable sensations after meals and a certain amount of irregularity in action of bowels, either diarrhea or constipation occur. The right sided growths rarely cause constipation due to fluid character of stool and the difference in character of growth on the two sides. The site of growths is remarkably constant. Therefore the operations for removal have become well standardized. There are three types of growths encountered, the most malignant being the hard, craggy ulcer. The annular or ring type often met with on the left side and the fungating or palpable type are less malignant.

Urinary Antiseptics.—YOUNG (*Jour. Urol.*, 1924, 11, 19) says that the best way of combating infections both general and local would be by intravenous injection of harmless chemicals. The author feels that the near future will find surgeons using this method for not only acute septicemias, otherwise fatal, but for serious chronic local infections, such as those encountered in the urinary tract. During the World War surgical results were transformed and thousands of lives saved by the progress made in the use of antiseptics. The advances in germicidal drugs since the war has been greater and has already transformed the therapy of infection in many specialties. The deep seated infections of the urinary tract are more difficult to cure but already much has been accomplished.

Experimental Closure of Large Bronchi.—BETTMAN (*Arch. Surg.*, 1924, 5, 418) states that the pleura of the dog has a strong resistance to infection. His dogs died from pneumothorax. Lobectomy does not kill the dog. The animal survives the operation and within a short time is in as good health as before. The cut bronchus heals readily and firmly, but the healing is brought about by peribronchial tissue. The removal of an entire lung is technically easy. The dogs recover quickly from the operation, but almost invariably die in five days.

Operation Shock.—FRASER (*Brit. Jour. Surg.*, 1924, 11, 410) remarks that operation on a case which shows persistent low blood-pressure should be delayed if possible until means have been taken to raise the blood-pressure. The operative procedure should be as short as is consistent with thoroughness. The least possible interference and trauma should be done. Every effort should be made to avoid unnecessary loss of blood. Chilling the patient before, during or after the operation must be avoided. If it is possible to exercise a choice of anesthetic, nitrous oxide and oxygen should be chosen. If simple restorative measures have failed to raise the blood-pressure, it should be raised by intravenous infusion of human blood, or 1 pint of 6 per cent gum acacia solution in normal saline. If examination of the blood shows that a condition of acidosis is present, a reserve alkali should be built up by the intravenous infusion of 1 pint of 4 per cent solution of sodium bicarbonate.

Case of a Retroperitoneal and Perinephric Infection (Abscess) Treated by Intravenous Injection of Mercurochrome.—YOUNG (*Johns Hopkins Hosp. Bull.*, 1924, 25, 14) states that the remarkable results obtained with mercurochrome intravenously in septicemias prompted the author to use it in recent cases in which urethral and vesical instrumentation was followed by fever, gradually increasing pain and tenderness on left side reaching to the left kidney area. The detailed results record that a colorimetric method can be used to determine the strength in which mercurochrome after intravenous injection may appear in urine, stools and vomitus. A strength of 1 to 10,000 was maintained in the voided urine for three hours, and also in stools. The immediate sharp febrile reaction from the instrumentation followed by a rapid fall to normal and the disappearance of definite symptoms and signs of a retroperitoneal abscess from the mercurochrome injection seem

to verify previous animal experiments which show a pronounced general and local germicidal effect from intravenous injections of mercurochrome.

Diverticulum of the Urinary Bladder.—JUDD and SCHOLL (*Surg. Gynec. and Obstet.*, 1924, 38, 14) claim that diverticula occur most commonly at the prostatic age, while the most common site of the outlet is in the region of the ureteral outlet. Diverticula were completely excised in 50 cases (series of 132 cases). Three patients died. In 37 cases in which there was obstruction of the vesical outlet, the diverticulum was excised and prostatectomy performed. In 46 cases the diverticulum was not removed. The ureter was involved in the diverticulum in 5 cases. In 20 cases the diverticula were associated with stones. Carcinoma occurred in the diverticulum in 4 cases. Three died shortly after operation, while the fourth lived sixteen months.

Knock-knee and Bow-leg.—SIMON (*New Orleans Med. and Surg. Jour.*, 1924, 76, 329) says that knock-knee and bow-leg are by far the most common of deformities of the lower extremities, and comprise fully 15 per cent of all cases in Orthopedic Clinics. Bow-leg is the most frequent of the two, in most statistical records. Both deformities are more commonly found in the male than in the female child. At two periods of life do these two deformities most often develop, in early childhood, and in adolescence, when rapid growth may lessen the stability of supporting structures. Rickets is the basic etiology. The treatment of both conditions may be considered under three heads: Expectant or constitutional, mechanical, and operative. In bow-legs, the seat of operation is usually the tibia, in knock-knee, the fracture must be made in the femur above the condyles. Support for considerable periods is necessary.

Endothermy in the Treatment of Accessible Neoplastic Diseases.—WYETH (*Ann. Surg.*, 1924, 79, 8) says that desiccation was devised and has been so brilliantly developed by Clark of Philadelphia. The desiccation spark is not hot enough to carbonize, but is of sufficient heat to cause rapid dehydration of the tissue, rupturing the cell capsule and converting the area treated into a dry mass. Moreover this method destroys tissue without opening blood or lymph channels and will act as a styptic when there is oozing of blood. It is impossible to overestimate the importance of the fact that with endothermy the growth is removed as a necrotic mass instead of as a group of viable cells. An important difference between endothermy and all other methods of cauterization by heat is that in endothermy the active electrode is cold when applied. Heat comes from within by the resistance of the tissues to the current. The three most important neoplastic tissues, tuberculosis, benign and malignant neoplasms, and syphilis all yield to this treatment. Cases are cited in full through article.

Brain Abscess with Pathological Observations.—BAGLEY (*Surg. Gynec. and Obst.*, 1924, 38, 1) has arranged the avenues of infection in 4 groups: The extradural extension of the primary focus, with protrusion of the distended dura into the cranial cavity; secondary

invasion of the brain along the bloodvessels without extradural link; penetrating brain injury with infection by foreign body, deep, with or without stalk; abscess superficial and open, secondary to direct laceration and infection of the brain tissue. The author classifies the abscess walls as follows: Dense, fibrous, mesoblastic tissue wall; fairly firm wall containing some fibers proliferated from neighboring mesoblastic tissue; walls of varying thickness the result of glial proliferation; and walls showing no evidence of a protecting reaction. The clinical course of a brain abscess varies according to the infecting organism, the channel through which this organism reaches the brain, and the location of the infection in the brain substance as regards mesoblastic and epiblastic tissue.

Simple Ulcers of the Jejunum and Ileum.—BROWN (*Edin. Med. Jour.*, 1924, 31, 45) says that simple ulcers are rare in these anatomical parts. It is, however, more frequent in the ileum than in the jejunum. The ulcers are rounded, clean-cut, with punched out edges, and tend to be terraced, the mucosa suffering more extensively from the necrotic process than the serous coat. It is not clear, however, whether the ulcer is primarily due to the elective localization of the bacteria or whether there is some alteration in the intestinal wall, which offers a suitable nidus for the organisms. The presence of gastric mucosa in abnormal situations has been offered as cause for such simple ulcers.

Carcinoma of the Papilla of Vater.—ABELL (*South. Med. Jour.*, 1924, 17, 24) states that carcinoma of the papilla of Vater is usually slow of growth and late to give rise to metastasis, yet there are few situations where cancer so promptly gives evidence of its presence or so quickly devitalizes the patient. The author has had the unusual experience of 3 operative cases, which he analyzes at length. The first case lived for two years after the second operation. The terminal symptoms indicated obstruction of the duodenum, with metastases in the liver. The second patient is still alive three years and six months after operation, and four years after onset of symptoms. The lumen of the ampulla is so small that the growth causes symptoms almost coincidental with its appearance. Pancreatitis was present in these 3 cases, but they showed no glycosuria. Studies of the literature showed that transduodenal extirpation of the papilla was performed eighteen times, with 7 deaths and resection of the middle duodenum four times, with 2 deaths. Retroduodenal extirpation of the distal end of the choledochus, inclusive of the papilla three times, with 2 deaths. Excision of the papilla from the dilated choledochus through inversion once with operative recovery. It would appear that best results follow the radical removal in two stages: A preliminary cholecystenterostomy, with later transduodenal excision, suturing common duct mucosa to the intestine at point of division.

Studies on the Ureter and Bladder (with Especial Reference to Regurgitation of the Vesical Contents).—GRAVES and RAVIDOFF (*Jour. Urol.*, 1923, 10, 135) state that regurgitation is an experimental fact. The conditions that favor its occurrence, however, have been less well understood and it is with these that the authors were particularly

concerned. In the case of normal rabbits it was found that ease of regurgitation depended upon many factors. The chief one among them was good bladder tone which seemed to be indispensable. It was learned that those bladders which were relatively empty and contracted at the beginning of the preparation produced reflex twice as frequently as those which had been recently distended with large amounts of urine. In the series in which the ureters had been rendered abnormal reflex occurred just as frequently as with normal structures and in cases where one ureter alone was distended the occurrence of regurgitation did not differ in its essentials on the two sides. The conclusion was therefore reached that the degree of ureteral activity has relatively little bearing upon regurgitation. The authors have never seen antiperistalsis in a normal ureter and in no way have they found it concerned in regurgitation. In spite of experimental difficulties reflex has occurred as a result of acute urinary obstruction. The authors have demonstrated that regurgitation of vesical contents into the ureter may be observed in the normal, intact, unanesthetized subject. Their final conclusion is that bladder regurgitation may be accountable for ascending infections of the urinary tract, particularly in cases of vesical neck obstruction.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

A Clinical Study of Rickets in the Breast-fed Infant.—DEBUYS (*Am. Jour. Dis. Child.*, 1924, 27, 149) in this series considered only those cases in which the symptoms were noted before complementary feedings were instituted. Cod-liver oil was not given in any case before there was unmistakable evidence of the existence of rickets. Lack of supervision and care seemed to cause the rickets to develop with more intensity. There was no noticeable increase in the symptoms after simple acute illness, but there seemed to be a direct relation between the severity of the rickets and the interval of non-supervision. There was no apparent relation between the severity of the rickets and the numerical order of the child in a family, or the number of children in a family. Syphilis was noted in only 8 instances as determined by clinical manifestations of the disease, and the Wassermann reaction. There was apparently no relation between syphilis and the severity of the rickets. The atmospheric conditions during the period of the study showed that the amount of sunshine was greater and the temperature higher than the normal average, and that the humidity was the normal average. According to the clinical manifestations of rickets, the disease was present in every case in the study. The disease was more marked in the colored subjects than in the white. There was no seasonal peak of the individual symptoms. There was a seasonal peak

of the combined symptoms noted in the month of March. Costal beading was the most frequent symptom. Enlarged epiphyses, cranial bosses, flaring ribs, and craniotabes followed in the order named. The short period of the existence of craniotabes, with its abrupt decline, was striking. Each symptom was more common in the colored than in the white. Beading showed the least difference. The difference increased as the frequency of the individual symptom decreased with the exception of craniotabes. Rickets should not be looked upon as a disease of the second half of the first year, but as a disease which may begin shortly after birth. In the study of the influence of rickets on the growth and development of the child it was seen that the heights of the white babies were normal average, but the heights of the colored babies were below normal average. The weights of the white babies were a little above the normal average. The weights of the colored babies varied so much for the different ages that they were too unsatisfactory for comparison. The weights of the markedly rachitic were below the normal average. While there was some slight variation in the measurements of the head, the most significant was the increased size of the head in the markedly rachitic colored babies. The chests of the colored babies were smaller than the average normal. The abdomens in this study were smaller than the normal average. In the markedly rachitic the abdomens were larger than the average normal. Tissue turgor was recorded as excellent only in the white. It was as poor more frequently in the white than in the colored. Dentition began earlier in the colored, and at the end of a year the average number for the colored was greater than for the white. Aside from the fact that the colored with the mildest rickets had more teeth and had them earlier, nothing was noted in the study as to the influence of the severity of rickets on dentition. A study of muscular development as reckoned by the ability to sit alone, stand alone and walk alone showed some slight variations between white and colored. It showed nothing between the least marked and the most marked cases of rickets.

A Study of Three Hundred Cases of Pertussis in a Hospital.—HERRMAN and BELL (*Arch. Pediat.*, 1924, 41, 13) found that the females were more frequently affected with pertussis than the males. Eighty per cent of all cases of pertussis occur in children under five years of age. The largest number of cases of the disease occur during the summer months, at a time when the other communicable diseases are at their lowest ebb. Every spasmodic cough is not whooping-cough. There are cases of pseudopertussis. The term pertussis should be restricted to an acute infectious and communicable disease, caused by the Bordet-Gengou bacillus. Pertussis is most communicable in the catarrhal stage, when its true nature is not recognized. It is usually not communicable after the fourth week. In a series of 297 cases, the duration of the disease was from five to twelve weeks in 70 per cent of the cases. In 80 per cent the whoop lasted from one to four weeks, and in 86 per cent the vomiting lasted from one to four weeks. The Bordet-Gengou bacillus is regularly present in the catarrhal stage of the disease. The respiratory complications are by far the most important. They are present in 58 per cent of the series. Fourteen per cent had a complicating bronchopneumonia. The earliest and most characteristic change in

those patients who have bronchopneumonia is the presence of localized fine resonant rales at the base or at the angle of the scapula especially on the left side. The susceptibility and the unfavorable progress of pneumonia in infants is probably due to immunologic not to anatomical peculiarities. There is no conclusive evidence that pertussis is an important factor in the causation of tuberculosis of the lungs. A positive Pirquet reaction does not become negative in the course of the pertussis. The principal aids in the diagnosis of pertussis are the presence of a relative and absolute lymphocytosis in the blood; the presence of the Bordet-Gengou bacillus in the sputum and a positive complement-fixation test. The cutaneous tests have not proved of any value. The prognosis in pertussis depends on the age of the child and on the presence or absence of pulmonary complications. There are more deaths from pertussis among females than among males. Eighty per cent of all deaths from pertussis occur in children under two years of age. The greatest mortality occurs in the late winter and early spring, and is largely due to intercurrent catarrhal infections which cause pneumonia. In a series of 297 cases 90 per cent of the deaths were due to a complicating pneumonia. The mortality in those patients who had pneumonia was 18 per cent. The mortality in those who had pertussis and measles was 30 per cent. Pertussis is difficult to control because it is most communicable in the catarrhal stage, when its true nature is not recognized. In selected cases treatment in a hospital is necessary and advisable. The cough is not the only or the most important symptom of the disease. The nervous system and the nutrition are affected. Patients with this disease should be kept in bed. If possible the bed should be placed in the open air. Meteorological conditions seem to have an effect on the paroxysms, for patients may show changes in the frequency and the severity of the cough from day to day, irrespective of the treatment. In the control of the spasmodic cough, antipyrin fortified by the bromids has given the best results. The authors did not obtain favorable effects from injections of ether or from vaccination. Pertussis vaccine has a specific effect in about one-fourth of the cases. In those who fail to respond the vaccine may have been given too late, or the Bordet bacillus is not the cause. When a case of pertussis occurs in an institution for children an autogenous vaccine should be prepared and used for immunizing and treating.

Acute Infections of the Urinary Tract.—Pyelitis.—HOPPE (*Arch. Pediat.*, 1924, 41, 29) says that this disease is not a clinical entity. Cystitis, ureteritis, calculi, pyelitis, pyelonephritis and renal abscess all give the same clinical findings by our present day clinical methods. Inflammation of the pelves themselves occurs in two forms, one of which involves the mucous membrane, and the other the submucosa and the peripelvic tissue. There are three routes of infection. It may ascend through the lumen of the ureter. It may ascend through the lymphatics around the ureters. The infection may be hematogenous, the bacteria localizing in the capillaries of the pelvic peripelvic tissues. The symptomatology is varied. Fever of obscure origin is most common. The diagnosis rests upon the finding of pus or bacteria in large quantities in the urine. Hexamethylenamin seldom gives good results in treating this condition. When it does act favorably it is probably

because the infection is chiefly in the bladder. The alkali group gives the most uniformly beneficial results. The sodium salt is best. The mode of action is not clear, but it is probably due to several factors such as diuresis, rendering the urine non-irritating and possibly the stimulation of leukocytic action and antibody formation. Foreign protein such as horse serum intramuscularly has been recommended in treating chronic cases. Vaccines are unreliable, but should be given a trial in obstinate cases.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

The Wassermann Reaction in Diabetes.—ROCKWOOD and SANFORD (*Am. Jour. Syph.*, 1923, 7, 679) report the results of Wassermann tests on 501 patients with diabetes, 201 by the Noguchi and 300 by the Kolmer technic. They conclude that there is only a coincidental relation between syphilis and diabetes in their series. False positives are rare in diabetes and do not exceed in number the proportion that would normally be expected as falsely positive in the types of technic employed by various authors.

The Roentgenotherapy of Pointed Condyloma.—SCHOENHOF (*Arch. f. Dermat. u. Syph.*, 1923, 142, 380) directs attention to the superiority of roentgen-ray treatment over cautery and surgical ablation in the treatment of extensive and persistent condyloma formation about the genitalia, both in men and women. The report is based on 12 cases observed from six months to one year since cure. Papillomata within the urethral orifice and vagina responded, as well as those on the surface. It is necessary to employ a dosage just below the erythema limits and 3 to 4 mm. aluminum filtration with epilation in most cases, but no ill-effects were noted in any case. The relief afforded the foul vegetative cases is striking.

Syphilis in the Bechuana and Native.—MCARTHUR (*Brit. Jour. Dermat.*, 1923, 35, 411) discusses the peculiarities of syphilis in the South African native, whose rapid syphilization is destined to provide a health problem of considerable magnitude for the future. The most notable points made by the author are: The absence of visceral lesion; the absence of neurosyphilides; the high incidence of tardive heredosyphilis; the chronicity of isolated lesions; "wit-kop," the favoid syphilide of the scalp. He remarks on Brock's observation that syphilitic fibrosis of the lung is exceptionally prevalent, and agrees with him as to its occurrence, although he finds it less common than Brock reports it (35 per cent). The author feels that syphilis markedly predisposes to tuberculosis among the natives. Neuro-

syphilis is unknown, and this exemption is by no means due to the absence of alcohol, as suggested in the case of the Arabs, for the Bechuana native is a heavy user of alcohol. Heredesyphilis is enormously prevalent and produces a marked reduction in physique. Hutchinsonian teeth are unknown, but mulberry molars take their place. In spite of the high incidence of familial syphilis, abortion and miscarriage are rare, and wholesale unrestricted marriage among infected and heredesyphilitic persons is the rule. The influence of physiological defence in recovery from syphilis is well illustrated by the response of many lesions simply to rest and feeding, without any attempt at specific treatment.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Acute Salpingitis.—Most of the American gynecologists have assumed the attitude that the last word has been said in the matter of the treatment of acute salpingitis and for some years past they have been content to allow all of these cases to subside before considering the propriety of operative intervention. It will no doubt be somewhat of a surprise to the gynecologic surgeons on this side of the water to hear the views expressed at a symposium devoted to this subject in the section of Obstetrics and Gynecology of the 1923 meeting of the British Medical Association (*Brit. Med. Jour.*, September, 1923, p. 399). In the introductory paper, BOURNE advises operation at the earliest possible moment, that is, as soon as the disease is diagnosed as a suppurative salpingitis. At operation in this stage the tubes are greatly congested and plum-colored, with edematous fimbriæ and pus leaking from the abdominal ostium; plastic lymph adheres in flakes to the peritoneal surface of the tubes and neighboring viscera, such as the ovaries and uterus. Organized adhesions have not yet had time to form. Bourne states that each tube should first be slit up as far as possible along the border opposite to its mesenteric attachment, the pus very gently swabbed away, and the mucous membrane carefully inspected. Should it appear intact to the naked eye, only congested without ulceration or grayish patches of necrosis, the tube should be left *in situ* without any further treatment beyond a few sutures of thin catgut to fix the mucocutaneous surfaces at any point where there is arterial bleeding. Any cyst in the ovaries should be opened freely to prevent the formation of an ovarian abscess; a drainage tube is placed to the bottom

of the pouch of Douglas, and the abdomen is closed, or drainage may be provided through the vagina. The advantages which Bourne claims for laparotomy and salpingostomy are (1) that a check is given to spreading peritonitis and the formation of adhesions and peritoneal abscesses by opening and draining the pelvis; (2) the laying open of the tube drains its lumen and immediately offers it the chance of resolution without the risk of further permanent changes caused by a continuation of suppurative inflammation and (3) salpingostomy obviously renders the formation of a pyosalpinx impossible, and permanent thickening of the tubal wall extremely unlikely. If after laying open the tube, the mucous membrane shows gray patches of ulceration and gangrene it is beyond the power of functional recovery and should be removed. The only possible object of preserving the tubes is to maintain their function, and if this appears impossible owing to the extent of their destruction the tubes should be completely removed. By this operation there can be no further salpingitis, and the ovary is saved considerable risk of infection. To leave the tube alone and merely drain the pelvis is to invite the formation of chronic tubal disease and permanent ill health, with a long convalescence and possibly disturbed by residual abscesses. How far it is usual for so complete resolution to follow acute suppurative salpingitis with the crowning success of a subsequent pregnancy it is impossible to state for probably nobody has yet done sufficient operations of this kind, but cases are on record of pregnancy following salpingostomy of the tube in a chronic state and Bourne believes it is reasonable to expect similar success in the acute stage if operated upon early. If however, salpingostomy does fail to produce resolution and a functioning tube, no harm has been done by not removing the tube, since it cannot lead to a chronic pyosalpinx. At this meeting BONNEY stated that for many years he had been an advocate of operating upon all cases of salpingitis at the earliest possible moment. It has been suggested that patients operated upon early have frequently to be reopened on account of collections of pus in the ovaries or pelvis, but he has never had to do this. While not denying that an inflamed tube may recover sufficiently to allow the occurrence of pregnancy, he is of the opinion that such complete recovery is rare. His experience with conservation with drainage has not been particularly encouraging. All of his cases recovered, but one nearly died of paralytic ileus, and none of them has conceived since the operation, while in 2 cases he had to reoperate on account of chronic disease of the appendages. The operation above described appeals to Bonney as being much more likely to lead to complete restoration of the tubal function, but one must remember that though it makes future closure of the abdominal ostium less likely, it can have but little effect on the uterine end of the tube. Early operation is exceedingly safe when the tubes are removed, and evidence seems to show that the risk is not greatly increased by conserving the tubes. He believes that a pyosalpinx or an ovarian abscess is a disgrace to the surgeon if the delay which allowed such formation is due to his advice. The parallel with appendicitis is a fair one. There the surgeon seeks to operate before abscess formation because the operation is safer than after an abscess has formed. In salpingitis also, the operation is safer before abscess formation, but in salpingitis there is an additional reason for early operation. No one wants to conserve an

appendix, healthy or unhealthy, but the ovary is a different matter, and now evidence is suggested that the tubes may be saved if operated on early enough. Natural cure of a pyosalpinx or an ovarian abscess is usually effected by adhesion to the pelvic colon with discharge of the pus into the bowel. Relief is not immediate as a rule, for there are generally two or more collections of pus and moreover the abscess cavity at once becomes analogous to a blind internal fistula with fecal infection of its walls and contents so that prolonged suppuration with intermittent discharges of pus anum is not uncommon. In delayed operations the surgeon frequently has to dislodge a tube or ovary which has already perforated into the bowel with the result that a fecal fistula up to the drainage tract develops within the first few days. This is an important objection to delayed operation and a valid reason in favor of surgical interference at the earliest possible moment. Finally, as a reason for immediate operation, there is always the possibility of faulty diagnosis. There are cases of pelvic appendicitis, diverticulitis and also early extrauterine gestation, which are impossible at the outset to distinguish from salpingitis. Continuing the discussion, BLAIR BELL stated that undoubtedly some mild cases of gonorrheal salpingitis recover spontaneously. In most cases however, he does not believe that the operation suggested will effect a cure since the interstitial portion of the tube will generally be occluded. Moreover, he doubts whether incision of the tube will lead to the disappearance of the organisms located in the mucosa which is a site of election. In answer to Bourne's proposal to perform salpingectomy to save the ovary from infection, he states that if a tube be enlarged and adherent it is extremely difficult to remove it without damaging the blood supply to the ovary. In such circumstances, when pregnancy is impossible, he performs ovarian grafting. PHILLIPS, in the concluding paper of the symposium, expressed the opinion that the tubes should be conserved, whether this be accomplished by medical treatment or by operation and slitting the tubes since even though the tubes are damaged by acute salpingitis, they still have a conceptional value. The closed ostial end can be reopened and the patency of the tubes established. He has performed reconstructive operations upon the tubes in 20 cases complaining of sterility and 5 of these (25 per cent) have become pregnant. The types of operations performed in these cases were (a) salpingostomy, (b) partial salpingectomy, (c) resection and anastomosis, (d) incision and resuture after canalization. It is hoped by the editor that the reader will understand the foregoing to be merely a report of the views of some of our British colleagues and by no means a personal endorsement. The subject is of considerable interest, although as yet largely theoretical, but further work in this field should be encouraged in suitable cases until sufficient evidence accumulates that its value may be truly estimated.

Results of Treatment of Bladder Tumors.—In reviewing 380 cases of vesical tumor YOUNG and SCOTT (*New York Med. Jour.*, 1923, 118, 262) found that 80 per cent of bladder tumors occur between forty and sixty-nine years of age, being about equally distributed in these three decades. Both papillomata and carcinomata are much more frequent in the region of the trigone and ureteral orifices and adjacent lateral walls of the bladder and vesical neck. The anterior wall is less frequently involved and the vertex and upper posterior wall are much

more rarely involved. The vertex, anterior, upper lateral and posterior walls are most suitable for resection and excellent results may be expected by radical removal of a wide margin of bladder wall, while good results may be obtained by resection in the base of the bladder and region of the ureters. When the vesical neck is involved, deep cauterization is more effective than excision. Fulguration is the method of choice in benign papilloma, but in large tumors radium is of great assistance in causing a rapid disappearance of the tumor, and owing to the potential malignancy of all vesical papillomata, radium should generally be applied, if possible. In malignant papillomata, radium applied with an operative cystoscope and held in position with a clamp fastened to the table, is of first value and gives more brilliant results. Here again the conjoint use of fulguration and radium is advisable. The same treatment is sometimes completely effective in papillary carcinomata. Where the tumor is definitely malignant or very extensive, particularly if infiltrating, it should be attacked suprapubically, great care being taken not to touch the tumor or break off any papillary processes, and alcohol or 20 per cent resorcin applied to destroy any that may have dropped into the bladder or wound. If resection can be carried out successfully with a wide area of healthy bladder wall, whether extraperitoneal or transperitoneal or with transplantation of a ureter, it should usually be done, but the operation should not be so extravagantly extensive as to face a very high mortality rate. The position of radium implantation is still *sub judice*. A few brilliant and remarkable cases are reported and they have had some, but always associated with deep and widespread cauterization. Viewed as a whole however, the gloomy outlook which was held as to the curability of bladder tumors has passed. Fulguration, radium, the electrocautery and careful radical resection have transformed the situation, so that now about 95 per cent of the benign and 75 per cent of the malignant papillomata, about 50 per cent of the papillary carcinomata and somewhere near 25 per cent of the infiltrating carcinomata are probably curable by one or more of the methods above referred to. Young and Scott state there is no phase of surgery in which during the last ten years more gratifying advance has been made than in that of tumors of the bladder.

An Antiseptic Pyelographic Medium.—Although they were convinced that 12 per cent sodium iodide solution was the best pyelographic medium that had been suggested, CUNNINGHAM, GRAVES and DAVIS (*Jour. Urol.*, 1923, 10, 255) deplored the fact that it had no antiseptic properties and they conducted an investigation to overcome this one drawback. After consideration of all possible antiseptics they decided the 1:3000 mercuric iodide in 12 per cent sodium iodide is the most satisfactory. They found that this solution has a phenol coefficient of 0.033 and when used in equal amounts with a colon bacillus infected urine, it destroyed bacterial growth in two and one-half minutes. They have employed it routinely in their clinic and have observed no immediate or subsequent ill-effects or discomfort, following its use either in the bladder or renal pelvis, even in the presence of acute inflammation. The addition of the antiseptic sacrifices in no degree the value of the medium from the standpoint of the roentgen-ray density. They believe that the use of this solution reduces to a minimum the risk of introduc-

ing infection and furthermore it provides some degree of positive benefit, apart from diagnosis, in cases in which infection already exists. The solution is prepared by dissolving 1 gm. of mercuric iodide in 3000 cc of 12 per cent sodium iodide. The latter is made with chemically pure sodium iodide and distilled water. The final solution does not need to be boiled.

Microscopical Compared with Clinical Diagnosis of Uterine Cancer.—Most investigators recognize the value of making a routine histological examination of all neoplastic tissue removed at operation but NORRIS (*Am. Jour. Obst. and Gynec.*, 1923, 5, 1) has undertaken a study at the Laboratory of Gynecological Pathology of the University of Pennsylvania with a view to checking up with the actual figures the relative values of this procedure among the different types of malignant tumors. He found that cancer of the cervix can generally be diagnosed correctly by clinical methods since in his series of 253 specimens, 81.4 per cent were diagnosed positively by the clinician, 11.4 per cent were suspected and in only 2.3 per cent was malignancy unsuspected by the clinician. In contrast to this, of the 101 cases of fundal carcinoma that were studied, no fewer than 20 were clinically diagnosed as benign, 57 were positively diagnosed by clinical means, and an additional 24 were suspected of being malignant. Thus about 20 per cent were of the unsuspected variety, which in itself is sufficient evidence to prove the necessity for making routine histological examinations. Even after removal of the uterus, cases will be occasionally encountered that will prove puzzling until they are subjected to microscopical examination. Of the entire series of 101 cases of carcinoma of the fundus, curettings alone were submitted to the laboratory in 58 cases. Of these the clinical diagnosis was positive in 21 or 36.2 per cent, the clinical diagnosis was doubtful in 22 cases and in 15 cases (25.8 per cent), it was benign. Norris is unable to give the figures as regards the frequency with which the clinical diagnosis of malignant tumor was made but which proved to be benign, although he believes it a considerable group. Of 35 malignant connective-tissue tumors, only 8 appear to have been degenerations of previously benign neoplasms and since 1216 fibromyomata were removed during this time, the incidence of sarcomatous degeneration of myomata in this series was about 0.6 per cent. In confirmation of the correctness of the microscopical examination in the myomata and sarcomata it may be stated that follow-ups have been made on both and none of the myomata have had recurrences and over 80 per cent of the sarcomata have succumbed. The diagnosis of chorionepithelioma from the curettings alone is often impossible. Some specimens are so clearly malignant that a positive histological diagnosis is entirely justifiable, but many cases do not fall within this category. Norris states that this is appreciated by all gynecological pathologists, but is not fully recognized by clinicians at large. Summarizing the entire series of 391 cases of malignant tumors, it is found that the clinical diagnosis was correct in 272 cases (69.3 per cent); the true condition was suspected in an additional 59 cases (15 per cent); in 15 (3.8 per cent) the clinical diagnosis was of malignant tumor, but the type of neoplasm was not recognized, and in 45 (11.5 per cent) the condition was clinically regarded as benign and its true character determined only on histological examination.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

The Influence of the Suprarenal Cortex on the Gonads of Rabbits.—

I. THE EFFECTS OF SUPRARENAL INJURY (BY REMOVAL OR FREEZING) ON THE INTERSTITIAL CELLS OF THE OVARY.—As it is recognized that hypertrophic changes occur in the interstitial cells of the ovary, and in the suprarenal cortex, in certain animals during pregnancy, and, likewise that the removal of the gonads causes hypertrophy of the suprarenal cortex, JAFFE and MARINE (*Jour. Exper. Med.*, 1923, 38, 93) conducted numerous experiments with the idea of ascertaining the effect which suprarenal injury might produce on the sex glands. Of the 30 rabbits which were subjected to double suprarenalectomy, a moderate or marked ovarian enlargement was observed in 76 per cent of those surviving the operation over thirty days. The ovarian enlargement consisted essentially of an hypertrophy of the interstitial cells. Twelve of the 13 rabbits, upon which a partial suprarenalectomy was performed, presented normal sized ovaries. The authors believe that "the hypertrophy of the interstitial cells is a compensatory reaction and adds further data to the functional interrelation between the suprarenal cortex and the interstitial cells."

II. THE EFFECTS OF SUPRARENAL INJURY (BY REMOVAL OR FREEZING) ON THE TUBULES AND INTERSTITIAL CELLS (LEYDIG) OF THE TESTES.—In a companion publication, the same investigators (*Jour. Exper. Med.*, 1923, 38, 107) studied the effects of double suprarenalectomy on the testes of 48 rabbits and of partial suprarenalectomy on the tests of 45 rabbits. Contrary to the marked hypertrophy which occurred in the interstitial cells of the ovary, it was found that there were no specific changes either in the tubules or in the interstitial cells of the testes after double or partial suprarenalectomy. The authors state that "these facts indicate that the interstitial cells of the testes and ovary are not functionally homologous."

Diphtheritic Vaginitis in Children.—Having found 26 cases of diphtheritic vaginitis in children in searching the available literature for the last thirty years VAN SAUN (*Jour. Infect. Dis.*, 1923, 33, 124) concluded that diphtheria of the genitals in children was uncommon and that primary genital diphtheria was rare, occurring only six times. The authoress reported a case, as developing in a girl of six years, who developed a membranous vaginitis thirty-seven days after a nasal culture yielded diphtheria bacilli. Although antitoxin was given and local treatment was instituted immediately, the child was very ill,

being unable to walk for three months. Positive cultures were obtained from the vulvar membrane for forty-two days, at the end of which time the diphtheria bacilli disappeared. About two months after the onset of the vaginitis, one positive throat culture was obtained. The organisms were found to be virulent and fermented dextrose. Since her recovery the child has remained in perfect health. In the cases collected from the literature, there were 4 deaths and the disease persisted from one to four weeks, as a rule.

Immunological Significance of Vitamins. Influence of the Lack of Vitamins on the Production of Specific Agglutinins, Precipitins, Hemolysins and Bacteriolysins in the Rat, Rabbit and Pigeon.—To determine the effect of a deficiency of vitamins A and B on the production of agglutinins, precipitins, hemolysins and bacteriolysins, WERKMAN (*Jour. Infect. Dis.*, 1923, 32, 247) chose, as the animals for experimentation the rat and rabbit, because they are susceptible to a deficiency of vitamin A, and the pigeon, which is susceptible to the lack of vitamin B. Appropriate diets were used to produce xerophthalmia in the rats and rabbits and polished rice was given to the pigeons to cause polyneuritis, *Bacillus typhosus* served as an antigen in the production of agglutins, which were detected by a modified Dreyer technic. Human serum was used as antigen in the precipitin tests in the rats and *Bacillus typhosus* in the production of bacteriolysins in the rats and rabbits. Rabbit corpuscles were employed in the production of hemolysins in the rat and rat erythrocytes served as antigen in the rabbit. After divers controlled experiments with a large number of animals, it was found that rats and rabbits lacking vitamin A or B, showed no difference in their ability to produce agglutinins, precipitins, hemolysins or bacteriolysins. Pigeons, showing a deficiency of vitamin B, also were able to produce agglutinins. The author concludes that it is reasonable to believe "that cataphylaxis in animals suffering from the lack of vitamins is not the result of the destruction or paralysis of the antibody-forming mechanism that produces agglutinins, precipitins, hemolysins or bacteriolysins."

Influence of Lack of Vitamins on Resistance of Rat, Rabbit and Pigeon to Bacterial Infection.—Continuing his observations, WERKMAN (*Jour. Infect. Dis.*, 1923, 32, 255) conducted a series of experiments to ascertain the influence of vitamins A and B on the natural resistance of the rat, rabbit and pigeon to infection. As both the rat and pigeon, and, but to a lesser extent, the rabbit, are normally immune to anthrax *Bacillus anthracis* was selected for inoculation, as well as a diplococcus resembling the pneumococcus, which was recovered from the lungs of a moribund rat. All experiments were controlled. The leukocytes and erythrocytes were counted independently. Blood platelets were determined by the Buckman and Hallisley method and the coagulation time of the blood was arrived at by use of the Brcdie-Russel-Boggs coagulometer. During the course of the experiments, respiratory infections were noted in rats lacking vitamin A. In addition, 0.2 cc of a living eighteen-hour broth culture of *Bacillus typhosus* killed 3 of 4 rats lacking vitamin A, while none of the controls died. It was learned that rats and rabbits lacking vitamin A became less resistant to infection

the test, for the third time, a wheal developed with redness which disappeared slowly. Later tests induced the same sequence of reactions. It was suggested by Goodall that the successive crops of serum rash represent separate reactions to sera, of different horses, which may have been pooled. This explanation is improbable because pooled pseudoglobulins have not been observed to produce recurrent attacks; because serum from one horse has produced recurrent endermal reactions; and because there is more convincing evidence that successive crops are the manifestations of successive appearances, at different time intervals, of sensitiveness to the different serum proteins—the explanation proposed by Dale and Hartley and substantiated statistically by Coca. There is ample evidence that euglobulin, pseudoglobulin and albumin are endowed with readily distinguishable antigenic properties. All of the recent investigations have disclosed the fact that the three proteins differ considerably in their antigenic "activities." These diminish with increasing solubility in ammonium sulphate solutions; euglobulin is the most active fraction, albumin the least active. Larger doses of albumin are necessary to sensitize and to shock guinea-pigs than is the case with euglobulin. The latent period before hypersensitiveness develops is appreciably longest with albumin. Incidentally, as Coca has shown, precipitin for egg globulin is produced earlier than for egg albumin. Davidson has recently conducted a detailed investigation of the various forms of serum rash and their relation to the proteins of whole horse serum. He recognizes three kinds of rash, urticarial, morbilliform and circinate; he considers that the diffuse erythematous type is probably due to scarlet fever. The average day of appearance of the rashes following injection is as follows: Urticarial, the ninth; morbilliform, the twelfth; circinate, the fourteenth. There being these three types of rash, and three dominant specific varieties of proteins in whole horse serum, Davidson concluded that each protein acts specifically in the human body to produce a certain type of rash. His correlation is as follows: Euglobulin produces the urticarial type because in experimental animals sensitiveness to euglobulin develops soonest, and because when concentrated serum is employed, with removal of euglobulin (and albumin) the urticaria is almost totally eliminated. The latter contention may be disputed; Park states that with regard to concentrated serum the later the development of the rash the more likely it is to be urticarial in nature. Sensitiveness to albumin develops latest and therefore probably causes the delayed type of circinate rash. Pseudoglobulin probably causes the morbilliform eruption. Thomson also reports that the circinate rash develops late and is more frequent after a previous urticaria. A triple reaction to horse serum has been shown by Hooker to be due to specific hypersensitiveness, to serum albumin, euglobulin and pseudoglobulin. Thereby, he believes the evidence that these proteins are severally and specifically concerned with the manifestations of recurrent serum is strengthened.

An Epidemiological Study of Folliculosis of the Conjunctiva.—VELDEE (*Pub. Health Reports*, 1923, 38, 2877) noted the difficulty of diagnosis of this condition, particularly in the differentiation from trachoma, and states that treatment and observation may be necessary

before a decision is arrived at. The rate among school children is much higher than has been reported for trachoma. The disease is most prevalent at five and six years having practically disappeared before twenty is reached. Social and economical conditions do not appear to be etiologically related. Size of family, sex, and nutritional conditions appear unimportant. Diseased tonsils appear to predispose to folliculosis. Errors of refraction have no marked influence. The concluding paragraph of this paper reads: "From the foregoing study of folliculosis it seems reasonable to conclude that it is an affection of early childhood, occurring somewhat more frequently in children with hypertrophied tonsils, developing no symptoms, running a very brief course as compared with trachoma, and disappearing spontaneously without sequelæ."

Diphtheric Vaginitis in Children.—VAN SAUN (*Jour. Infect. Dis.*, 1923, 33, 124) states that a recapitulation of the cases of diphtheric vaginitis in children in the literature shows the relative infrequency as well as the rather indifferent reports of many of them. Primary diphtheria of the vagina is said to have occurred but 6 times in a series of 26 cases, and in some of these cases it is not quite clear but that a more extended examination might not have revealed another avenue of infection. Apparently, bacteriological examinations were made in 15 of the cases; virulence tests were made in but 6 of these. A number of the cases occurred in children physically below par. The mortality does not seem to have been higher in diphtheric vaginitis than in other forms of diphtheria. Four deaths were reported in the series collected. The duration of the disease would seem to have been anywhere from one to four weeks, as a rule. No mention is made of release cultures in any of the reported cases, although they may have been taken. The experience in the case reported by Van Saun indicates that they are quite as advisable after diphtheric vaginitis as after any other form of diphtheria infection. That several negative cultures obtained were followed by many positive cultures gives point to various articles on diphtheria carriers which have drawn attention to the well-known fact that two negative cultures are by no means conclusive evidence that the patient will remain free from diphtheria bacilli for even a short period of time.

The Elimination of Carbon Monoxide from Blood by Treatment with Air, with Oxygen, and with a Mixture of Carbon Dioxide and Oxygen.—SAYERS and YANT (*Pub. Health Rep.*, 1923, 38, 2053) give the following summary of their paper:

1. Recovery from carbon-monoxide poisoning depends to a great extent upon early elimination of carbon monoxide from the blood.
2. The rate of elimination of carbon monoxide from the blood depends upon the percentage of oxygen in the air breathed, also upon the rate and depth of respiration.
3. Pure oxygen causes the elimination of carbon monoxide about four times as fast as normal air, when breathed by persons who have been gassed until 35 or 40 per cent of the hemoglobin in their blood has been combined with carbon monoxide.

4. Breathing a mixture of oxygen containing 8 to 10 per cent of carbon dioxide causes deep and rapid respiration.

5. Breathing a mixture of oxygen and carbon dioxide (8 to 10 per cent) causes the elimination of carbon monoxide about five to six times as fast as normal air, when breathed by persons who have been gassed until 30 to 40 per cent of their blood has been combined with carbon monoxide.

6. It is recommended that all victims not under a physician's care be caused to breathe oxygen in the purest form available for at least twenty to forty-five minutes.

7. It is recommended that physicians use the carbon dioxide oxygen mixture where possible, and note the results, but when the mixture is not available that they use pure oxygen.

Efficacy of Botulinus Antitoxin.—The Public Health Service (*Pub. Health Reports*, 1923, 38, 2966) quotes from Hygienic Laboratory Bulletin No. 136 as follows: The discrepancies in the literature regarding the identification of the organisms concerned in the production of botulism and the isolation of a new type by the author prompted a more complete investigation of the so-called "botulinus" strains than has hitherto been attempted. The strains studied include representatives of different groups, particular attention being given to type C. The properties of toxin and antitoxin of organisms concerned in botulism are discussed at length, based on the author's experiments. As a result of these and prior investigations, an antitoxin has been elaborated and standardized. The author states that the curative effect of antitoxin in human cases has not been determined definitely, but that it seems reasonably certain that the antitoxin is effective prophylactically as is tetanus antitoxin. As to the effects produced when administered after symptoms develop, no certain statements can be made, owing to the fact that spontaneous recoveries of patients showing definite symptoms of botulism have been recorded. The curative properties are dependent upon the length of time elapsing between the consumption of the food and the administration of the antitoxin, and also on the amount of toxin which has been ingested. The most promising field for the use of the antitoxin is in outbreaks of botulism in which persons who have consumed food containing the toxin have not developed symptoms, or only slight symptoms. In any case, the use of antitoxin is indicated, since it is the only known specific remedy and the possibility always exists that the results may be favorable.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL*.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript*.

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1924

ORIGINAL ARTICLES.

CLINICOPATHOLOGICAL STUDY OF A SERIES OF CASES OF
ACUTE MENINGO-ENCEPHALITIS.*

BY QUINTER O. GILBERT, M.D.,

OAKLAND, CALIF.,

AND

ADELINE E. GURD, M.D.,

ANN ARBOR, MICH.

DURING recent years an abundant literature has accumulated dealing with the disease Lethargic Encephalitis. Few of the contributions that have appeared have concerned themselves with detailed studies of the histopathology of the disorder or the problems of differential diagnosis. With this in mind we have made a study of a selected number of fatal cases of various forms of acute meningo-encephalitis, in order to contribute to the differential diagnosis of these disorders and to direct attention to some clinical errors that have come to our notice, where laboratory studies and post-mortem examinations have not been used to confirm the diagnosis.

Further, a correct understanding of the underlying pathological changes in the central nervous system may aid in a better knowledge of the late clinical manifestations that are now of such importance in the care of residual effects of this disorder.

During the spring months of 1920, there occurred in the vicinity of Detroit a considerable epidemic of lethargic encephalitis. In all there were about 100 cases. During this time there came into

* The clinical observations were made in the medical division of the Receiving Hospital, Detroit, Mich. The pathological studies are by Dr. Gurd, laboratory of Neuropathology, State Psychopathic Hospital, Ann Arbor, Mich.

the Receiving Hospital a considerable number of acute cases of cerebral disorder of various types usually in extremis, or when the disease was well advanced. A selected series of these cases in which autopsies were obtained forms the basis of this contribution. The autopsy in all cases was made a few hours after death.

The brains were fixed in 10 per cent formalin and at once sent to the laboratory of neuropathology, at the State Psychopathic Hospital, Ann Arbor, Mich., where they were studied by Dr. Gurd. The results of the histopathological studies are given in connection with the presentation of each case and are summarized at the conclusion of this contribution. The material studied was from a wide range of regions. Each region was studied in preparations following the methods of Alzheimer, Bielschowsky, Klarfeld-Achucarro, Herxheimer and Weigert. This made possible a broad survey of the various reactions in specific tissues in a very complete way.

CASE I.—S. G., male, aged thirty-one years, was admitted in a semicomatose condition with signs of meningeal irritation. The only information available was that for several weeks he had been sick with fever, headache and general weakness, but had kept at work until a week ago. Four years previously while in the Greek Army he had both gonorrhea and syphilis. Examinations showed him to be under-nourished and considerably dehydrated. The chest showed a definite impairment of both upper lobes with bronchovesicular breathing and increased moisture throughout the lung area. His temperature (rectal) varied during his illness between 99° and 103°; pulse-rate ranged between 80 and 120; respirations from 20 to 40.

Neurological Examination. The pupils were unequal and did not react to direct or consensual light. The intrinsic eye muscles were normal. Accommodation could not be accurately determined. The head and neck were held rigidly. The patellar and Achilles reflexes were absent. Tests for the reflex responses of Babinski, Oppenheim, and Chaddock gave no reactions. None of the superficial skin reflexes could be obtained. Kernig's sign was always elicited, and there was flaccid paraplegia of the lower extremities. No response was obtained to deep pin pricks over the entire body. The urine was retained, and there was apparent loss of rectal control.

The urine showed no abnormal findings. The blood showed 13,000 white cells. The differential count was: Polymorphonuclear cells, 73 per cent; large lymphocytes, 10 per cent; small lymphocytes, 7 per cent; large mononuclear cells, 6 per cent; transitional forms, 4 per cent. Wassermann examination was negative on the blood. Two lumbar punctures were made. In both the fluid was under increased pressure. There were at the first examination 260 cells and at the second 200 cells. There was a strong ++++ globulin reaction (Pandy). The curve of the mastic test at one examination

was 221100. The cells were nearly all of the large mononuclear type, and many showed marked ameboid movements.

At the second lumbar puncture he was given a reinjection of mercurialized serum, and an intravenous injection of 0.4 gm. of arsphenamine. There was a slight improvement for one day, after which he relapsed into unconsciousness. The eyes were rolled upward with slight divergent strabismus.

Autopsy. Examination of the brain showed adherent dura mater and marked congestion of the small vessels of the pia mater. No tubercles were observed in the gross inspection. The lungs showed old tubercular infiltration with caseation in both upper lobes. The remaining organs showed no marked gross abnormalities.

Microscopical Examination. Lungs showed an old thickening of the pleuræ with infiltration of both lungs by active tubercle formation of varying size and age. The liver showed increase in fibrous tissue with diffuse congestion. The kidneys showed marked congestion with a moderate grade of chronic nephritis.

Central Nervous System. Gross inspection of the brain after several weeks hardening in 10 per cent formalin solutions showed marked injection of the meningeal vessels. The pia-arachnoid was turbid, especially over the sulci. The lateral ventricles were widely dilated. The choroid plexuses of the lateral ventricles were cystic and calcareous. The ependyma of the fourth ventricle was coarsely granular.

Microscopical study showed all portions of the pia-arachnoid involved in a meningitic process, tubercular in type, characterized by a dense infiltration by small lymphocytes, plasma cells, polyblasts and macrophages, occasional giant-cells containing from 2 to 25 nuclei and tubercle bacilli in many areas. Very little connective-tissue increase was observed. Here and there the inflammatory process assumed an irregular round "tubercle" form.

The bloodvessels showed no alteration of either adventitial or elastic coats. The endothelial cells showed some swelling at times, but more commonly shrinking and detachment from the vessel wall. The adventitial lymph spaces of the meningeal vessels were much distended and packed with plasma and lymphocytic cells. This infiltration followed the vessels of the pia into the cortex for a very limited distance, becoming gradually lessened in density until it disappeared. The capillaries and deeper cortical vessels showed no infiltration. The meningitis was much more severe in the medulla and pons, and the infiltration of the adventitial lymph spaces of the vessels continued into the substance of the medulla and pons to a very considerable distance and many small inflammatory foci were seen at a distance from the surface; *e. g.*, foci were noted in the olives, in the third nerve nuclei and in the lenticular nuclei.

The ependyma of the third ventricle, the aqueduct of Sylvius and of the fourth ventricle showed much proliferation and the inflammatory process in many areas had invaded the subependymal regions, occasionally forming foci of some extent in both thalami and caudate nuclei. Many portions of the choroid plexes showed inflammatory infiltration by plasma cells and small lymphocytes.

A very marked glial reaction was observed in the molecular layer of the cortex near infiltrated vessels wherever they passed into the nerve tissues and in the neighborhood of the inflammatory foci noted in the lenticular nuclei, medulla, etc. The majority of the proliferating cells showed much increase in the size of the fibers and the nuclei were already undergoing regressive changes, the nuclei being small, pyknotic and irregular in form. An occasional ameboid cell was seen. No rod cells were observed.

The cortical nerve cells showed, in general, acute swelling, but many were in a more advanced state of degeneration, some in complete disintegration. Many of the smaller pyramidal cells were dark and turbid in hue, the nuclei also being of the same color. The protoplasm was broken up into granules. The nuclear membranes were either jagged and irregular or indistinguishable from the surrounding protoplasm.

Small hemorrhages were seen in the pons, and diapedeses in the basal ganglia.

Pathological Diagnosis. Chronic tuberculosis of lungs; congestion of kidneys; moderate chronic nephritis; mild cirrhosis of liver; acute tubercular leptomeningitis; infiltration of cortical vessels of a chronic inflammatory type; multiple tubercular encephalitic lesions in basal nuclear structures; chronic inflammatory reactions of choroid plexuses; perivascular progressive glia reactions in the cortex; degeneration of nerve cells of cortex of the type of acute swelling; multiple miliary hemorrhages in the pons.

CASE II.—S. C., male, aged twenty-seven years. Two weeks prior to admission the patient noticed pains in the left shoulder and arm. This subsided until two days before coming to the hospital, when there developed an acute onset with fever, drowsiness, diplopia and pains in the left arm with muscular twitchings about the lower thorax and upper abdomen.

On examination the patient lay in bed in a lethargic state. When aroused he attempted to answer questions, but his responses were slow. He was conscious of having wet the bed on the night previous. The lungs were negative; the heart showed a slight left-sided hypertrophy with accentuation of the second aortic sound. The abdomen was negative except for slight suprapubic fulness. His blood-pressure was 175/100.

Neurological Examination. The pupils were contracted, reacting sluggishly to light and accommodation. Both eyelids drooped, but

could be elevated voluntarily by wrinkling the forehead. No extra ocular muscular change was present; no facial paralysis. Biceps and triceps reflexes were present. Umbilical and cremasteric reflexes questionable. The patellar reflex was lost, but the Achilles was present. The Gordon and Oppenheim tests produced no response; Babinski's and Chaddock's reactions were absent, but plantar stimulation caused a marked tremor of the lower extremities. There was more or less constant contraction and twitching of the abdominal muscles which was somewhat less marked in the arms. There was no paralysis, Kernig, or rigidity of the neck. It was necessary to catheterize the urinary bladder.

Two days later the pupils were much contracted. There was no response to light nor to tests for accommodation. The patellar, Achilles, biceps, umbilical, epigastric and cremasteric reflexes were lost. There was a bilateral external rectus palsy. Twitchings of the thoracic and abdominal muscles together with a "diaphragmatic jerk" were present. No response could be obtained to stimulation of the soles of the feet. Questions were answered very incoherently and in an unclear manner.

Two days after the above examination, the patient voluntarily called for a urinal and mentally was much clearer. Neurologically, however, there was no definite change. Three days later, the patient was still much clearer mentally, talked freely but was disoriented as to time and place. He said he felt as though "he was doped." He realized that he was somewhat mixed in his statements and that his memory was poor.

From this time, the patient gradually entered into a deep stupor from which he could not be aroused. When stimulated he tried to articulate but speech was inaudible. The right pupil was contracted to a pin-point, while the left was slightly larger. Neither reacted to light nor in accommodation. The biceps, triceps, umbilical cremasteric and patellar reflexes continued absent. The Achilles was present but diminished. There was involuntary bowel movement and urination.

The urine examination showed a specific gravity of 1025, a definite reaction for albumen, and the sediment showed a few granular casts.

The blood examination showed 10,000 white cells, 75 per cent polymorphonuclears, 5 per cent large lymphocytes, 11 per cent small lymphocytes, 5 per cent large mononuclears, 4 per cent transitionals. The blood Wassermann was negative. The blood incoagulable nitrogen was 0.042 gm. per 100 cc.

The spinal fluid ran freely. It was clear and contained 50 cells per c.mm. on first examination, and on a later examination 20 cells; these were small mononuclear cells. The first examination showed but a trace of globulin, the second a slightly larger amount. The Wassermann was negative. The mastic reaction was 110000.

Clinical Diagnosis. Meningo-encephalitis, lethargic; chronic nephritis.

Autopsy. Autopsy showed a marked congestion of the meninges, which were thickened and definitely adherent to the skull. The encephalon was very red, due to dilation and congestion of all the small vessels. The accessory sinuses were negative. The lungs were negative. The heart showed considerable left ventricular hypertrophy, with the aorta in good condition. The kidneys presented a granular surface when the fibrous capsule was stripped, together with secondary contraction. All other organs were negative.

Microscopical Examination. This was negative except for sclerosed glomeruli, dilation, thickening of the bloodvessel walls, and congestion in the kidneys. Otherwise there was nothing definite of note.

CENTRAL NERVOUS SYSTEM. The brain at autopsy was noted as very wet and cherry-red in color, and on later inspection it was unusually dark yellowish. The meningeal vessels were much congested and the meninges over the sulci and particularly over the base of the brain were turbid and opaque. Slight dilatation of the lateral ventricles was present.

Microscopical Examination. This showed all the bloodvessels extremely congested. Some of the large meningeal veins were thrombosed, one of which was beginning to organize. Hemorrhages into the pia-arachnoid were seen over the pons and cerebellum but no hemorrhages or diapedeses were seen in the nerve tissues in any portion examined. The adventitial coat of the vessels was unaltered, the elastic appeared somewhat swollen, the endothelium, especially of the smaller vessels and the capillaries, was swollen and in many vessels was proliferating very rapidly, but instead of remaining in place, or forming new vessels, it appeared to desquamate and lie in the lumen of the vessels, sometimes forming real thrombi. No infiltrated foci were seen in the cortex, but the medulla showed a few scattered vessels with the adventitial lymph sheaths full of small lymphocytes, plasma cells and polyblasts. The cells filled rather loosely the distended lymph spaces and did not always form complete sheaths. The caudate and lenticular nuclei also showed one or two very small inconspicuous foci. On the other hand, the pons and peduncles, including the substantia nigra, and the third nerve nuclei, were literally riddled with large and small foci of infiltrated vessels. The locus ceruleus especially contained many foci and the capillaries here showed plasma cells bordering their walls. In addition to the comparatively recent inflammatory foci many small foci were seen, which were evidently the remains of an earlier inflammatory action. In these little foci the nerve cells were partially or entirely destroyed and a mass of glia cells and fibers filled the space.

The pia-arachnoid showed no widening beyond that caused by the distended vessels. Many portions of it seemed completely normal, but over the sulci there was usually some slight cellular infiltration by small lymphocytes, an occasional plasma cell and polyblast.

The nerve cells in general were edematous, the nuclei showing folding of the nuclear membrane. A good many axonal reactions were seen, but no destroyed cells except in the areas of inflammatory foci. There was no glial proliferation in the cortex, but cells were seen here and there in both gray and white matter in regression, with very small irregular nuclei.

In the areas where more recent inflammatory foci occur there was some slight proliferation of glia cells, the nucleus being large and rather clear and the body large and pale staining. Around the foci of older date, the small scars spoken of above, both cells and fibers were increased. A good many rod cells were seen in the diseased areas of the pons and peduncles.

No alterations were seen in myelin sheath or Bielschowsky's stain, except in the Alzheimer-Mann's stain which showed some myelin balls and swollen and discolored axis cylinders in the diseased areas. Many amyloid bodies were seen in the margins of the pons and peduncles.

Pathological Diagnosis. Chronic nephritis; cardiac hypertrophy; acute congestion of pia-arachnoid; endarteritis of meningeal vessels, with multiple thrombosed vessels; hemorrhages in pia-arachnoid; disseminated encephalitic foci in medulla and brain stem and diffuse and focal degenerative changes in cortex and nuclear collections; localized progressive glia reactions in regions of encephalitic areas; pathological process of lethargic encephalitis.

CASE III.—P. F., male, aged forty-nine years. The patient was conscious, but because of the involvement of the face and neck muscles in particular, he could talk but little. He stated, however, that he had been feeling ill "generally" for about three days. The day before entrance, he was awakened by a pain in the right side and lumbar region; later his jaws and neck muscles stiffened until he had to lie with his head retracted, and could barely separate his teeth when attempting to open his mouth. He had some cough, no headache, chills or vomiting. There was no history of trauma or of taking drugs.

The patient was a large, well-nourished man, lying in bed with his head retracted. He was conscious and attempted to answer questions. When the command was given to open the mouth and protrude the tongue, the tip was caught between the teeth by a spasmodic contraction of the masseter muscles.

Neurological Examination. The function of pupils and extrinsic muscles of the eyes were normal. There was a marked stiffness of the neck and lumbar muscles. There was no Chvostek. The muscles of the face and neck were tetanically spastic. The biceps, triceps and patellar reflexes were slightly increased. The Babinski was persistently present on the left side. Oppenheim and Gordon reflexes were less positive. The umbilical and cremasteric reflexes were normal. No sensory changes were found.

The lungs were negative except for rales at the base. The heart was negative except for an accentuation of the second aortic sound. The abdomen was negative to palpation. Blood-pressure 140/80. In the examination of a small specimen of sputum no tubercle bacilli were found.

The temperature varied from 99° to 100°; pulse about 100; respiration 30.

The urine examination showed nothing abnormal. The blood examination gave 16,500 white cells. The blood Wassermann was negative. The spinal fluid was under pressure, and clear; there were 300 medium sized mononuclear cells per c.mm. and a trace of globulin. The Wassermann was negative. The mastic was 110000.

The patient developed difficulty in swallowing, became cyanotic and rigid throughout the body and died within twenty-four hours.

Clinical Diagnosis. The diagnosis was uncertain. Tetanus was suggested but no definite wound of entrance was found. The changes in the spinal fluid suggested an acute meningo-encephalitis of undetermined origin.

Autopsy. The cerebrospinal fluid was much increased. The meninges were adherent to the vault of the skull; they were quite thick and slightly nodular, without evidence of hemorrhage. The brain was markedly injected. The lungs showed marked anthracosis and a few calcareous and caseating tubercles at both apices.

The heart showed considerable thickening of the edges of the mitral valves, some sclerosis of the aortic valves, marked atheromatous changes in the ascending aorta and moderate left ventricular hypertrophy. The liver showed moderate enlargement with some increase in fibrous tissue. There was some chronic exudate over the spleen surface. The kidneys showed secondary contraction and a granular surface when the capsule was stripped. There were numerous old adhesions about the cecum.

Microscopical Examination. This showed old tubercles in the lungs, fatty degeneration and atrophy of the heart muscles, epicardial infiltration with round-cells together with early aortitis. The liver showed moderate degeneration with increase in fibrous tissue. The spleen showed atrophy, increased fibrous tissue and sclerosis of many bloodvessels. The kidneys showed sclerosis of the glomeruli and the tubular epithelium.

CENTRAL NERVOUS SYSTEM. On gross observation of the brain, an unusual slenderness of the basal vessels at once attracted attention. The internal carotids, communicating arteries and basilar appeared not more than half their usual size. Small sclerosed spots were also observed in all the basal vessels and on the branches in the fossæ Sulvii as far as they could be followed. Other agenetic features were present besides the lessened size of the bloodvessels. The Rolandic sulci cut into the Sylvian fissures, and many irregular and stellate depressions were seen at the junctions of the sulci.

Microscopical Examination. The meninges were negative. All bloodvessels were very full of blood, and occasionally a small hemorrhage was seen. The adventitial coats of most vessels were considerably thickened. The elastic layer in some of the larger vessels in the meninges of the medulla was thickened and split. Small effusions of blood were seen in the medulla and basal ganglia.

The nerve cells were all very edematous, the larger number having swollen, pale nuclei and more or less honeycombing of the body. Many cells showed Nissl's severe degeneration. In some the nuclei were dark colored and scarcely distinguishable from the rest of the cell. Large amounts of lipoid substance were present in most cells. The Betz cells and the larger pyramidal cells showed much less injury than the smaller cells and in some cases were normal. Axonal reactions were not seen. The glia cells did not seem increased in number, but many were much enlarged, but already showing regressive changes. An unusual number of "Füll-Körperchen" were seen in many areas.

Pathological Diagnosis. Pachymeningitis; chronic myocarditis; aortitis; hepatitis; sago spleen; congestion of the kidneys and moderate nephritis; chronic apical tuberculosis; agenetic anomalies in cerebral arteries, cerebral arteriosclerosis; diffuse degenerative changes in cortical nerve cells (Nissl's type of severe degeneration).

CASE IV.—Mc. M., aged twenty-eight years, laborer. Patient was brought to the hospital in an unconscious and delirious condition. No history of the past or present trouble was obtained.

The patient was a poorly-nourished negro, in a filthy condition. There were constant incoördinate movements of both arms, together with inaudible mutterings. Rotatory movements of both legs with flexion of the feet were constantly present. At times, he waved the arms about and picked at the bedclothes. There was considerable rigidity to passive movements of both arms and legs. The neck was stiff on rotation and flexed with difficulty. The left pupil was smaller than the right, neither reacted to light. The ocular muscles and accommodation could not be tested. The eyes showed no nystagmus. Both lids drooped without definite ptosis. The left corner of the mouth drooped. The biceps and triceps reflexes were questionable because of movements during the examination. The umbilical, cremasteric, patellar and Achilles reflexes were absent. Plantar stimulation caused no response. The Kernig was questionably negative. The legs, while not paralyzed, were more or less flaccid.

The lungs were hyperresonant on both sides with moist gurgling rales everywhere. The impairment was most marked over the posterior apices. The heart was negative, except for a soft systolic murmur. The abdomen was tympanitic with gas. The urinary bladder was distended. Catheterization was necessary. The tem-

perature varied from 100° to 102°. Pulse was 110 to 180 and respiration 30 to 60 at the time of death.

The urine was clear, specific gravity 1018, with a trace of albumin and a few red blood cells in the sediment.

The blood examination showed hemoglobin, 75 per cent; red blood cells, 4,000,000; white blood cells, 15,450; polymorphonuclears, 89 per cent; large lymphocytes; 4 per cent, small lymphocytes, 2 per cent; large mononuclears, 5 per cent; blood Wassermann, + + + + positive.

The spinal fluid was under pressure; globulin + + + +, cells 150; large and small mononuclears with many of the larger cells showing ameboid movements. Mastic 111000. The spinal fluid Wassermann was negative.

Autopsy. The meninges were markedly congested. The spinal fluid was excessive. Small whitish areas were present over the sulci and convolutions, but they were not of definite tubercle formation. All the small vessels were much congested. The pia was elevated, due to increased fluid beneath.

The right lung showed diffuse hypostatic bronchial pneumonia with small calcareous nodules at the apex, together with small abscesses. The left lung showed congestion and small nodules in the upper lobe. The heart showed scleroses of the coronary arteries and of the mitral valves, together with an early aortitis and definite atheromatous changes in the aorta. There were caseating glands about the pancreas and spleen and extension caseation into the edge of the spleen. The kidneys showed congestion and moderate secondary contraction. Definite tubercles were seen in both the spleen and the kidneys.

The microscopical examination showed many tubercles of varying sizes and age in the lungs. The lymph glands, spleen and liver showed many tubercles, some with caseation. The heart showed some albuminous degeneration of the muscle and there was early sclerosis of the aorta.

Central Nervous System. Microscopically, the pia-arachnoid drew immediate attention. It was not much widened between sulci, but many small lymphocytes, plasma cells and small and large phagocytes (macrophages) were seen in all areas examined. Over and in the sulci the infiltration was very dense and in many places breaking down of the infiltration mass was seen, indicated by the presence of many polynuclear leukocytes scattered through the mass and especially in the center of the mass. Many tubercle bacilli were seen in these areas.

The meningitis was most severe over the medulla, pons and peduncles, and vessels passing in from the meninges in these areas frequently showed considerable infiltration by plasma cells, small lymphocytes and polyblasts for some little distance from the margin of the section.

The ependyma of the aqueduct of Sylvius and the fourth ventricle showed much proliferation in many small patches, and in some areas it was infiltrated by plasma cells, lymphocytes and polynuclear leukocytes. In the gray substance around the aqueduct occasionally a focus of infiltration was seen around vessels. Focal infiltrations were also seen on the ventricular margins of those sections of thalami and caudate that were examined, and several rather large foci were seen scattered irregularly through the caudates. The portions of lenticular nuclei examined were free from foci. No foci were observed in the cranial nerve nuclei.

The choroid plexuses from the lateral and fourth ventricles showed dense infiltration into some of the villi by plasma cells, lymphocytes and phagocytes. The infiltration followed the vessels into the villi and occupied all the tissues of the supporting connective trabeculae and resulted in complete destruction of large numbers of the secreting cells. The plexus of the fourth ventricle was more involved than that of the lateral ventricles.

All bloodvessels were overfull with blood and occasionally there was an excess of polynuclear leukocytes and lymphocytes in their lumina. Their coats showed no alterations. The adventitial lymph spaces were much dilated and frequently packed with plasma cells and lymphocytes in the meningitis areas; especially in the small foci described above in thalami, pons, etc.

The nerve cells in the cortex were all edematous, showing folding of the nuclear membranes, and pale finely granular protoplasm. Many were much more severely altered, some appearing as fragments. Axonal reactions were rarely seen. Occasional myelin balls and swollen and discolored axis cylinders were shown by the Alzheimer-Mann's stain. The nerve fibrils were difficult to stain in Bielschowsky's stain, but when demonstrable showed slight change.

Satellitosis was increased. Both glia fibers and glia cells were in great excess in the molecular layer, where many very large proliferating cells were seen. The glia was increased to some extent in both white and gray matter aside from the molecular layer, and many ameboid cells were seen. Rod cells were seen in the cortex and also in the pons and peduncles. The nerve cells of the pons, medulla, and basal ganglia were edematous, but very few showed any severe degeneration. The subependymal glia was much increased, but proliferating cells were much smaller in size and more regular in form (small ovals) than the submeningeal glia.

Pathological Diagnosis. Chronic myocarditis; aortitis; pulmonary tuberculosis; chronic nephritis; tuberculosis of lymph glands, spleen and liver; tubercular encephalitis; granular ependymitis; tubercular meningitis; diffuse degenerative changes in nerve cells of cortex; progressive alteration in the neuroglia cells of the brain.

CASE V.—O. S., aged thirty-one years. The patient was very drowsy, mentally unclear and retarded in such a manner that a history other than that of a recent sore throat and a diplopia was unobtainable.

Examination. The patient was a well-developed male. He lay in bed stuporous or drowsy and was aroused with great difficulty. He mumbled incoherently in Polish. When stimulated by sharp commands such as, protrude the tongue, he put it first to the left then to the right with marked coarse tremors and twitchings. The arms were in almost constant motion. He often clutched both hands and had a decided tendency to pick at both the genitalia and his tongue. There was a marked drooping of the eyelids, more particularly of the right. The pupils were small and reacted sluggishly to light. The right pupil deviated to the right, while the left was centrally placed. The patient was able to elevate the eyelids when commanded to do so. Nasal and aural cavities were negative. There was no evident muscular paralysis. The neck was slightly stiff. The biceps, triceps and patellar reflexes were not obtained, Achilles slightly present. The Babinski, Oppenheim, Gordon and Kernig were negative. The superficial reflexes were uncertain because of marked muscular twitchings. These were present in the arm muscles and legs, but more marked about the lower thorax and upper abdomen.

The lung examination showed slight harshness of breath sounds, otherwise negative. There was moderate tachycardia of the heart. The abdomen was negative. Blood-pressure, 125/85.

The patient became more stuporous during the second and third day. He was almost insensible to pin pricks. The convulsive twitchings were more marked. There was a semihiccough in the convulsive twitchings about the lower thoracic and abdominal muscles and diaphragm. On the fourth day the patient was mentally more clear. He stated that he had been sick for five weeks with apparent hyperactivity and inability to sleep, together with severe pains in the arms and legs. He stated that his mind had been "foggy" and unclear, and that he had "seen double" many times. The following day he died from apparent cardiac exhaustion.

The urine examination was negative. The blood showed 10,000 white blood cells with 80 per cent polymorphonuclears, 10 per cent small lymphocytes, 2 per cent large lymphocytes, and 4 per cent transitionals. The spinal fluid was clear, it flowed freely. Globulin was present as a trace. The cells were 80 per cc, mostly small mononuclears. The spinal fluid Wassermann was negative. The temperature varied from 103° to 106°, the pulse from 120 to 150; respiration 30 to 40.

The *clinical diagnosis* was lethargic meningo-encephalitis.

Autopsy. Autopsy showed marked congestion of the meninges with increased cerebral spinal fluid. The brain itself was distinctly

red due to congestion. The lungs showed some adhesions about the left apex with a few old calcareous tubercles. The heart was normal; the aorta showed a few athermatous plaques in the lower portion. The aortic valves were somewhat sclerotic. The abdomen was negative except for a few adhesions about the gall bladder. The kidneys were negative, except for fetal lobulations. The spleen was somewhat contracted.

Microscopical Examination. This showed a few old tubercles in the lung tissue. The connective tissues of the spleen were increased. There was moderate inflammation of the kidneys.

Central Nervous System. Microscopically, the meninges of all portions examined showed small hemorrhages, which distended the membranes. These hemorrhages were most notable over the cerebellum. Aside from the widening caused by these hemorrhages, the meninges were very slightly increased in width in small patches where an infiltration by small lymphocytes and occasional plasma cells were seen. Here and there small patches of rapidly proliferating fibroblasts were seen, and in some areas granular cells were already filled with the débris from the small hemorrhages noted.

All the bloodvessels were congested. The adventitial coat as a rule showed no marked alterations, the elastic membrane was swollen. The endothelial cells were extremely swollen, and cells were frequently seen loosened at one or both ends and floating into the lumen of the vessel. Mitoses were occasionally seen in the endothelial cells. Polymorphonuclear leukocytes were seen occasionally in the lumina. No infiltration of the adventitial lymph spaces was seen in any sections of the cortex examined, but the portions of thalamus, lenticular nuclei, peduncles, pons, and medulla examined showed many small foci of plasma cells, small lymphocytes, occasional mast-cells and polyblasts around the smaller vessels, preëminently around the veins. The arteries as a rule showed no infiltration. Plasma cells were also frequently seen in the adventitial lymph spaces of the capillaries in greater numbers in the neighborhood of the above foci. An occasional polyblast, containing lipoid pigment, was seen in the adventitial lymph spaces. The lenticulars were involved to a much lesser extent than the thalami, pons and medulla, and the lesions were practically all in the globus pallidus. The substantia nigra showed more foci and of much larger size than in any other location, but the lesions were not limited to these areas. The third nerve nuclei were invaded.

The lesions in the medulla were very numerous and very diffuse, sparing, however, the olivary regions and the pyramids. Very small hemorrhages or more properly diapedeses were seen in the peduncles, medulla and basal ganglia. The locus ceruleus was especially riddled with small infiltrative foci, and foci were disseminated through all that portion of the pons dorsal to the median fillet.

The nerve tissues of the cortex, as a whole, showed severe edema, giving it a honeycombed appearance. The nerve-cell changes of the cortex varied greatly in the different layers. The small and medium-sized pyramidal cells showed severe acute alterations. The protoplasm was composed of fine granules, and the nuclei were frequently dark, discolored and irregular in form. The deeper cell layers showed much less alteration, the large motor cells were practically normal. The nerve cells in the basal ganglia, pons, medulla and peduncles on the other hand showed comparatively little alteration. A few nerve cells were destroyed by the immediate presence of an inflammatory focus, but others appeared quite normal.

Glia reactions were not very marked. Satellitosis was not increased. A certain number of ameboid cells were seen in the white substance, and in the thalamus and peduncles there were a few very small remnants of an older inflammatory process that showed as a lack of nerve cells and an excess of glia cells in the area, but none of the large actively proliferating forms of glia cells were seen.

Many amyloid bodies were seen scattered here and there in the neighborhood of the ventricles. The axicylinders in the neighborhood of the foci occasionally showed a swelling and tortuous outline, and myelin clumps and bodies were seen lying in the tissue. The nerve fibrils were unusually resistant to Bielschowsky's stain, but showed no other abnormalities.

Pathological Diagnosis. Old healed pulmonary tuberculosis; meningeal hemorrhages; acute leptomeningitis; acute proliferation and degenerative changes in cerebral bloodvessels; multiple focal encephalitic lesions in basal ganglia, pons and medulla; multiple miliary hemorrhages in basal ganglia; edema of cortex; localized acute degenerative changes in cortical nerve cells; pathological process of lethargic encephalitis.

CASE VI.—R. J., laborer, aged twenty-nine years. The patient was brought to the hospital because of his semidelirious condition. The only complaint was that of diffuse bodily pains.

Present Illness. Illness began about thirty days ago with soreness in the chest, general weakness and a feeling of being tired, headache and persistent pains up to a few days before entrance. At this time the pains became more aggravated, and the patient partially uncontrollable.

Examination. This showed the patient to be a well-nourished male lying in bed partially restrained. He was untidy and apparently semiconscious. He was partially aroused, however, at a sharp command, and was fairly well oriented and answered questions fairly well.

He had a diffuse burn over the chest, back and hips, together with a macular rash over the entire body, due to the reaction of mustard

plasters, which were applied previously, because of pain. There was a diffuse muscular twitching over the entire body, but more marked over the abdomen and lower thorax. He could not lie still because of the twitching. The most marked involuntary twitchings were about the face, right shoulder and lower thoracic muscles, together with a "diaphragmatic jerk."

The pupils were slightly contracted; they reacted neither to light nor in accommodation. There was no eye-muscle involvement and the tongue protruded straight. There was no facial palsy. The biceps, triceps, umbilica, cremasteric and patellar reflexes were absent. Oppenheim, Babinski and Chaddock gave no response. Kernig was negative.

Two days later there developed a marked external rectus palsy of the right, and less marked palsy of the left eye. All deep reflexes were absent. The patient was more unclear; he could scarcely be aroused. When he was aroused he carried out commands fairly well, many times he did not do so even when spoken to in his own language. The eyes were closed for the greater part of the time. The patient developed retention of urine. He became comatose and died on the following day.

The urine examination was negative. The blood examination gave 12,000 white blood cells with 68 per cent polymorphonuclears, 12 per cent lymphocytes, 14 per cent small lymphocytes, 4 per cent large mononuclears and 2 per cent transitionals. Blood Wassermann was negative. The spinal fluid flowed freely. It was clear, with 21 small mononuclears per cc. Globulin was present as a trace. The spinal fluid Wassermann was negative.

Clinical Diagnosis. Diagnosis was meningo-encephalitis lethargica.

Autopsy of the head only was permitted. The dura was adherent over the left side of the skull cap. The meninges were much congested. The brain itself was definitely red, due to the congestion of all the small vessels. The cerebral fluid was increased. Fluid from a ventricular puncture when cultured showed a diplococcus. The brain was preserved in 10 per cent formalin for detail study.

Central Nervous System. Macroscopically, the meninges and brain were very congested, the basal bloodvessels were somewhat lessened in size and contained small sclerosed patches. The pia-arachnoid was rust colored in places. There was a small hemorrhage at the anterior edge of the left internal capsule.

Microscopically, there were small foci scattered through the dorsal part of the medulla, in which the vessel walls were infiltrated with small lymphocytes, plasma cells and polyblasts. These often contained lipid substances. The capillaries in the thalami and basal ganglia were bordered by plasma cells. The bloodvessels as a whole showed no thickening of the adventitia, but showed swelling of the elastic and endothelial coats. Plasma cells were also seen along the capillaries in the thalami and subthalamic regions, in

the peduncles and in the gray substance of the pons. In the right caudate nucleus they were present in a few widely separated foci, and there were a few in the left globus pallidus. The vessels were all engorged and diapedeses had taken place in a few areas. A good deal of lipid material was seen along the lymph spaces, and in one arteriole in the right anterior central region a few small lymphocytes were seen in the adventitial lymph spaces. The fatty degeneration in the smallest arterioles formed at times a complete ring, every adventitial cell being degenerated. This condition was seen especially in the caudate and lenticular nuclei and in the peduncles.

The pia-arachnoid was thin and for long stretches perfectly normal, aside from the unusual distention of the bloodvessels. In some areas there was a very moderate degree of infiltration by small lymphocytes and polyblasts, the latter much in excess of the lymphocytes and mostly filled with pigment. Rarely a plasma cell was seen.

The nerve cells in the cortex varied very much in their pathology. Many of the largest cells were normal. Many cells showed acute swelling with pale, finely granular bodies and clear swollen nuclei; others were much more seriously affected, the nuclear membrane being folded and irregular and the nucleoli flanked by small satellites. Many axonal reactions were seen. No loss in myelin sheaths was observed.

Satellitosis was considerably increased and in the Mann-Alzheimer stain many pyknotic glia cells were seen, some having a ragged protoplasm. The nerve cells in the areas invaded by foci showed remarkably little alteration, only those cells in the focal area being affected. The glia in the affected areas showed considerable proliferation, but no very large cells, most of the cells being small, with fairly normal nuclei and small protoplasmic bodies.

Pathological Diagnosis. External pachymeningitis; multiple encephalitic lesions in medulla and basal ganglia; acute reactive and proliferative changes in cerebral bloodvessels; localized acute degeneration of cortical nerve cells; localized progressive glia reactions; pathological process of lethargic encephalitis.

CASE VII.—B. A., aged twenty-one years. There was no history other than that of pains in the head of one month's standing. The patient understood but little English and was primarily of low mentality.

On examination, the patient was a well-developed male lying in bed. He was so stuporous that he could only be aroused with the greatest difficulty.

There was no ptosis of the eyelids and no definite drooping, although the lids were held closed most of the time. The pupils were smaller than normal and reacted sluggishly both to light and in accommodation. The extrinsic muscles reacted normally.

There was no facial paralysis, perhaps a slight drooping of the left corner of the mouth. The tongue protruded straight; nasal and aural cavities were negative. The deep reflexes were all negative, the skin reflexes were apparently negative. There was a marked stiffness and rigidity to the neck muscles. Flexion and extension of the thigh and leg caused pain and stiffening of the muscles.

There was a definite tachycardia of the heart. The lungs showed some impairment, especially at the left apex, with definite harshness of the breath sounds over both upper lobes. The abdomen was negative except for suprapubic fullness.

Thirty cc of spinal fluid under considerable pressure was removed. This made the patient slightly more rational and to some extent relieved the headache.

The patient had a persistent retention of urine. The amount of urine obtained by catheterization varied from 1600 to 2000 cc in the twenty-four hour period.

On the fourth day in the hospital, 25 cc of spinal fluid was again removed, with slight improvement in the patient's condition.

On the seventh day of observation there was a definite change in the *neurological examination*. The patient responded somewhat better to commands. In the pupils no definite reaction could be observed either to light or in accommodation. The pupils were about equal, but somewhat smaller than normal. The right lid had a definite ptosis of small degree. A definite external rectus palsy on both sides was present. The facial movements were normal. The biceps and triceps reflexes were present but diminished. The patellar and Achilles were absent for the first time. The Oppenheim, Gordon, Babinski and Chaddock were normal.

Retention of urine persisted together with the increased volume. On the ninth day partial drainage of 45 cc of the spinal fluid was done with but slight improvement in the patient's condition. He died on the tenth day.

The urine showed a specific gravity of 1016, some albumin, a few pus and red blood cells in the sediment.

The blood report gave 3,900,000 red blood cells; 9000 white blood cells with 65 per cent hemoglobin; polymorphonuclears were 86 per cent; eosinophiles, 1 per cent; large lymphocytes, 1 per cent; small lymphocytes, 11 per cent; large mononuclears, 1 per cent. The blood Wassermann was negative.

The spinal fluid was clear on three occasions and showed 400, 450 and 230 cells per c.mm. The pressure and amount was always increased. The globulin was always heavy. The Wassermann on all occasions was negative. The cells were mixed large and small mononuclears. The large cells in many instances were definitely ameboid in character.

The temperature varied from 100° to 104°, the pulse gradually ascended from 70 to 140, respiration from 20 to 30.

An unsuccessful attempt was made to demonstrate tubercle bacilli in the spinal fluid.

Autopsy. This showed thickening of the meninges. There were no definite tubercles. There was a marked venous congestion of the pia. The cerebrospinal fluid was much increased, although fairly complete drainage was instituted the day previous. The brain gave the general appearance of redness from the injection of the small vessels. In the apices and the axillar region of the left lung there were fairly numerous, old, healed, miliary tuberculous nodules. The heart and aorta were quite normal. The liver was somewhat enlarged and congested. The spleen was grossly normal. Both kidneys were definitely of the "horseshoe" type. They were slightly enlarged, somewhat granular when stripped, with marked fetal lobulations. The gastrointestinal tract was normal. The *microscopical examination* showed the lungs to be congested and numerous miliary tubercles. The heart was negative except for cloudy swelling; pancreas was normal. The liver showed congestion, many tubercles were present in the spleen. The kidneys were congested together with dilatation of tubules and sclerosis of some of the glomeruli.

Central Nervous System. At the *autopsy*, the brain was white and showed extreme congestion of the meningeal vessels. The pia-arachnoid was opaque. There was moderate internal hydrocephalus.

Microscopically there were several small hemorrhages scattered through the pia-arachnoid. All portions of the pia-arachnoid that were studied showed a severe type of tubercular meningitis with many tubercle bacilli. The posterior velum, the choroid plexus of the fourth ventricle and the subependymal tissue of the basal ganglion showed vessels densely infiltrated by small lymphocytes, plasma cells and small and large phagocytes. The villi of the choroid plexus in the region of the inflammatory reaction showed partial to complete loss of the secretory cells. The ependyma was completely broken through by small glial proliferations.

The meningitis was very diffuse in all areas, but much more severe over the medulla, pons and peduncles. In the denser portions many polynuclear leukocytes were present. No giant-cells were observed. The vessels passing in from the pia of the medulla and in the raphé were infiltrated for considerable distance with small lymphocytes, but no plasma-cell infiltration of the capsule was seen, and mast-cells were absent. The vessels passing in from the region of the pons and peduncles were similarly infiltrated. There were foci, in which this infiltration was present, in the substantia nigra, in the third nerve nuclei, in the internal geniculate bodies and in the corpora quadrigemina.

Inflammatory foci were seen scattered through the thalami and caudates and to much less extent in the lenticular nuclei. The nerve cells in all portions of the central nervous system showed

lack of chromatin and a very few cells showed axonal reactions or stained a dark color. The glia in the cortex was negative except for some porliferative and regressive phenomena in the molecular layer. The subependymal glia was enormously increased, especially where infiltrated vessels were seen, and there was very marked glia proliferation on the margins of the medulla, pons and peduncles. The bloodvessels showed no thickening of their adventitial or elastic coats, but the endothelia was swollen, proliferating and frequently floating loosely in the lumen of the vessels.

Pathological Diagnosis. Chronic pulmonary tuberculosis; tuberculosis of the spleen; multiple hemorrhage in the pia-arachnoid; tubercular leptomeningitis.

CASE VIII.—A. B., female, aged twenty-three years. The patient stated that she first became ill about one month previous to our examination with severe pains in the head (frontal and occipital regions). Headaches and pains occurred periodically during the following weeks. At one time there was a severe pain in the foot for several days; later on similar pains were felt in the shoulder and arms. These pains recurred in various muscles of the body for about four weeks. The patient said she could not sleep at night more especially for the past week. She had been "sleepy all the time." For about one week "double vision" was present. At the time of examination she thought she saw her friends at the bedside at intervals and called to them and thought they touched her. Photophobia had been marked for about one week with definite drowsy feeling of the eyelids for three weeks past. At the same time there was a twitching of the muscles of the arms, legs, lower thorax and abdomen.

On *examination* the patient did not appear very sick although she picked at the bedclothes and closed the eyes as in a mild sleep, especially when her attention was not sharply stimulated. Apparently she was rational but mentally retarded. Her headache was located by placing the finger on the frontal and occipital regions. There was a definite drooping of the eyelids without definite ptosis. The right eye did not turn so far to the right as the left eye turned to the left. The pupils reacted sluggishly both to light and in accommodation. There was spasmodic twitching of the upper recti, midgastric, and the ninth, tenth and eleventh intercostal muscles. The biceps, triceps, umbilical, patellar and Achilles reflexes were normal. Plantar stimulation caused no response; no Kernig. There was a slight stiffness in the neck muscles when the head and neck rotated.

The lungs were negative. The heart-rate was increased. The abdomen was negative to palpation.

The patient gradually became weaker, respiration and pulse both became gradually accelerated. At the end of the first week

in the hospital there had occurred a definite progressive change in the *neurological examination*. At this time the pupils did not respond to light or accommodation tests. Both sides showed extra-ocular muscle palsies. The eyelids drooped, but were not paralyzed. There was a definite weakness of the left side of the face but the tongue was protruded straight.

The biceps and triceps reflexes, while present, were distinctly diminished on the right side. The umbilical and patellar reflexes were absent. The Babinski, Oppenheim and Gordon reflexes were normal on the right with no response on the left. Flexion of the head caused pain in the back of the head. There was a definite weakness of the throat muscles on swallowing and coughing. There was a spasmodic movement of both shoulder muscles, together with an irregular spasmodic movement about the diaphragm, not dependent on respiratory movements, and irregular twitching of the lower thorax was present on both sides. The chest examination was negative. Four days later the patient voided involuntarily. At this time the patient's heart became apparently much weaker. The *neurological examination* was about the same as before. Respirations were increased together with a "grunt." There was a general harshness of the breath sounds with diffuse moisture at the bases. The heart-rate was much increased and decidedly weaker, producing a thready pulse. A vesicular rash of the neck, head and chest was present, due to irritation and persistent and marked perspiration.

The urine was negative on repeated occasions. The blood showed 4,400,000 red blood cells; 13,250 white blood cells; 78 per cent hemoglobin; polymorphonuclears, 70 per cent; large lymphocytes, 10 per cent; small lymphocytes, 12 per cent; large mononuclears, 6 per cent; transitionals, 2 per cent. Blood Wassermann was negative. The spinal fluid was clear, under pressure, with a faint trace of globulin, 30 cells per c.mm. The Wassermann was negative.

Drainage of the spinal canal on two occasions relieved the headache temporarily, but this was only a transitory result. Patient died on the thirteenth day in the hospital from general, but chiefly cardiac exhaustion.

Clinical Diagnosis. Lethargic meningo-encephalitis.

Autopsy. The dura was found markedly adherent. The meninges were much congested. The vessels were dilated, but no nodules were present. The pia was distinctly cloudy, more dense than normal, and slightly elevated from the increased cerebrospinal fluid. The meningeal inflammation was probably greater at the base than over the vertex. The accessory sinuses were negative.

The lungs showed hypostatic congestion, with a small area of bronchial pneumonia. The heart was negative. The liver was negative. The kidneys showed fetal lobulation, otherwise negative. The ovaries, tubes, uterus, pancreas and spleen were normal.

Microscopical Examination. This was practically negative for other than slightly cloudy swelling, congestion and edema of all the organs.

CENTRAL NERVOUS SYSTEM. *Autopsy* showed a very edematous brain with extreme congestion of the meningeal vessels. The pia-arachnoid was not thickened or opaque, but showed many small hemorrhagic areas on the frontal and parietal lobes. The divisions of many sulci were agenetic in type.

Microscopically, the pia-arachnoid showed many small hemorrhages. Here and there were small areas of acute fibroblastic proliferation with a few small lymphocytes, plasma cells and polyblasts.

The bloodvessels were congested and frequently the whole lumen was packed with polynuclear leukocytes. The adventitial coats showed no alteration. The elastic membrane showed slight splitting. The intima was sometimes congested with many of its cells small and shrunken.

In the basal ganglia, peduncles, pons and medulla many vessels showed dense infiltration of the adventitial lymph spaces by small lymphocytes, plasma cells and polyblasts. While the veins were more frequently involved than the arteries, an occasional artery was seen with a moderate amount of infiltration. A very marked infiltration of the capillaries by plasma cells was also seen. These foci were scattered irregularly through the caudates and lenticulars. Foci were numerous in the third nerve nuclei, the substantia nigra and the anterior corpora quadrigemina. The foci in the medulla were mostly very small and lay near the ventricle. Several foci of old inflammatory lesions were seen in the medulla, the caudates, thalami and peduncles. In these areas the nervous tissues had disappeared and the space was apparently entirely occupied by glia fibers and cells. There was no marked glia reaction around the recent inflammatory foci. The glia in the cortex was somewhat increased in the molecular layer and many large spider cells were seen in the white matter along the border of the polymorphous cell layer.

The nerve cells of the cortex were unusually pale, but retained their form. The nuclei showed a breaking up of the nuclear substance with displacement of the pigment to the border of the nucleus. Sometimes this granular appearance of the nuclear pigment was so marked that it gave a small pyramid cell the appearance of a glia cell. In other cells the nucleolus was still present, but two or three satellite-like bodies were near it. The nerve fibrils showed no alteration in Bielschowsky's stain.

The nerve cells of the basal ganglia, midbrain, etc., showed very little alteration, except when directly involved.

Pathological Diagnosis. External pachymeningitis; hypostatic congestion of lungs; bronchopneumonia; cloudy swelling; edema and congestion of all organs; edema of brain; hemorrhages of pia-

arachnoid; focal proliferative changes in pia-arachnoid multiple; focal encephalitic lesions in basal ganglia, peduncles and medulla; diffuse degenerative changes in cortical nerve cells; pathological process of lethargic encephalitis.

CASE IX.—R. C., aged sixteen years. The patient was admitted in an excited delirious state. No definite history was obtainable except that a friend said she had complained of a sore throat a few days previous.

The patient on examination was actively agitated. There was no coöperation or response to questions. She was physically well-developed and negative on general examination, except for an increased heart-rate without other definite auscultatory findings.

Neurologically, the knee-jerks were questionably absent. Accurate data concerning the reflexes was impossible to obtain, due to the very generalized choreiform movements of the entire body, but more especially of the arms and face. It was necessary to restrain the patient with a sheet.

A small infiltration about the left elbow developed, from which a streptococcic pus was obtained.

The temperature (rectal) was constantly elevated, ranging from 102° to 104°. The heart-rate was regular and varied from 120 to 160. It gradually increased as the disease progressed.

The white blood cell count was 14,000; polymorphonuclears, 78 per cent; large lymphocytes, 9 per cent; small lymphocytes, 8 per cent; large mononuclears, 3 per cent; transitionals, 1 per cent. The urine (catheterized) was negative. The lumbar puncture was done, of necessity, under ether anesthesia. The fluid was clear, cells 3 per c.mm. The Wassermann was negative both on blood and spinal fluid.

Clinical diagnosis was chorea insaniens of acute streptococcic origin. The possibility of an acute form of lethargic encephalitis of the choreiform type, however, was suggested by the attending neurologist. The active muscular movements were considered to be of central origin, due to stimulation by irritation.

The patient died on the seventh day in the hospital, chiefly from cardiac exhaustion.

Autopsy (two-hour postmortem). Head: The dura was quite firmly adherent over the entire skull cap. The brain was markedly congested, grossly very red, with marked increase of fluid beneath the pia in the sulci. A right anterior ventricular puncture gave a slightly cloudy fluid, from which short-chained streptococci were cultivated. The accessory sinuses were negative. The brain was suspended in 10 per cent formalin for detailed study.

The lungs showed moderate congestion. The heart was but slightly enlarged. There were a number of fragile vegetations along the margin of the mitral valves. Cultures gave a short chained

streptococcus. The spleen was quite soft and congested. The organs otherwise were grossly negative. *Microscopically*, the heart valves showed a small round-celled infiltration with some degeneration and necrosis. The liver showed edema, congestion and the kidneys slight cloudy swelling.

At *autopsy* the brain was noted as very bright red, with many small submeningeal hemorrhages.

Microscopically, the most prominent element in the picture was severe edema of all the tissues, engorgement of all bloodvessels and hemorrhages. These were severe in and under the pia-arachnoid and of moderate degree in all other locations. In addition a small number of infiltrative foci of very small extent were seen. These never formed a real sheath around any vessel, and affected a small area only. The infiltrative cells were lymphocytes with occasional polyblasts. Many vessels were filled with white blood cells. The areas of predilection of the foci were: medulla, midbrain and thalami. Although the infiltrative foci were very small in extent and number, their seat was that usual in lethargic encephalitis and with the multiple hemorrhages, general edema, moderate nerve-cell degeneration and moderate glial reaction, formed a fairly characteristic picture of that disease.

CASE X.—A. J. The patient was a large adipose Lithuanian woman of approximately twenty-five years. She neither understood nor spoke English. She was brought to the hospital from a rooming-house by the police ambulance, because of a delirious mania said to have been precipitated by the desertion of a fellow countryman paramour.

Under observation she was continually excited, untidy, with no regard for her personal appearance. She sang incoherently and uttered baby-like calls. It was necessary to restrain her, and when so restrained in bed, she kept up continuous oscillatory, masturbatory movements, with a succession of short excitement periods.

Because of the excitement and resistance the physical examinations were never complete. On entrance there was no fever, axillary or rectal. The heart and lungs were apparently normal. There were unquestionable changes in the light reactions of the eyes. The reflexes could not be accurately determined.

Catheterized urine examination was quite negative.

The blood Wassermann was + + + + positive.

Under ether anesthesia a lumbar puncture was made. The fluid flowed freely. It was clear and contained 40 white mononuclear cells per c.mm. The globulin was + + + +. The Wassermann was positive with 0.8 cc and the mastic was 444432100.

Mercury intramuscularly, together with arsphenamine intravenously, and spinal drainage under anesthesia with the reinjection

of autogenous serum, did not apparently affect the course of her disease.

During the third week in the hospital the patient developed a slight fever and coincidently a purulent discharge from the right ear. As the patient did not speak English at all and Lithuanian only unintelligently and made no demonstration of having pain, middle-ear infection was not suspected. The left ear, on examination showed a bulging membrane.

With the coincidence of an acute infection and the exhaustion asthenia the heart quite suddenly became irregular and rapid. The temperature was 100° axillary. There was no definite clinical evidence of meningeal inflammation before death.

At *autopsy* the dura was slightly more adherent than normal over the vertex and at the base. The cerebrospinal fluid was increased. The pia was injected. There was no evidence of pus. The convolutions showed no gross atrophies.

The mastoid cells when opened were both filled with a seropurulent material. The accessory respiratory sinuses were negative.

Except for increase in body fat, some atheromatous plaques in the aorta and renal congestion, the general autopsy findings were negative.

Central Nervous System. The *autopsy* showed marked congestion of vessels of the meninges, the pia-arachnoid thickened and opaque, agenetic sulci, and granular ependymitis of the fourth and lateral ventricles.

Microscopically, wherever the pia-arachnoid was present, a more or less intense meningitis was seen. The fibroblastic elements showed some proliferation. There were large numbers of plasma cells, mast-cells, small lymphocytes and some polyblasts lying in the meningeal tissues.

The bloodvessels had practically normal coats, but the adventitial lymph spaces were much distended and often packed with plasma cells and lymphocytes. The capillaries in all parts of the cortex examined were infiltrated more or less by plasma cells. This infiltration was much more marked in the frontal than in other regions. Considerable lipid pigment was seen along the vessels. The bloodvessels of the raphé in the medulla, at the level of the twelfth nerve nuclei, showed some round-celled infiltration.

In the pons several densely-infiltrated vessels were seen in the fifth nerve nuclei, and in the midbrain plasma-celled infiltration of the capillaries was general. Infiltrated vessels were also seen in the third nerve nuclei, in the red nuclei and the substantia nigra. The ependyma of the aqueduct at this level was irregularly but markedly proliferated and showed infiltration by plasma cells and lymphocytes. Plasma-celled infiltration of the capillaries was not so general at this level as in the pons.

Infiltrated vessels were seen scattered through the thalami and

the caudate nuclei, and in the caudates in particular there was very general plasma-celled infiltration of the capillaries, much more than in the anterior central and calcarine areas.

There was no loss of nerve cells and the individual cells showed remarkably little severe change. In general, they were very pale, the chromatin which remained being in fine granules. The nuclear membranes were folded and the nucleoli were frequently broken up into small fragments, and when a distinct nucleolus was still present, as in the majority of cells, there were two or three small accessory bodies. Fatty degeneration was slightly in excess of the normal. No alterations were seen in Bielschowsky's fibril stain.

The fibrous glia was much increased, especially in the molecular and polymorphous layers, and large numbers of glia cells in all areas showed regressive alterations, the nuclei being small, pyknotic and irregular in form. By the Alzheimer-Mann stain many spider cells of unusual size were seen. Rod cells were present in large numbers, and many of these presented transitional forms, some bent at an acute angle, others showing a branching of the protoplasm at one end, etc. Ameboid cells were not seen.

Pathological Diagnosis. Acute purulent mastoiditis; early cardiovascular syphilis; subacute leptomeningitis; chronic meningo-encephalitis; histopathological reactions of general paresis.

CASE XI.—A. W. The patient was a white male, aged twenty-one years. No definite history was obtained, as he was taken from a room in a semicomatose condition by the police. It was said that there were gas fumes about his room.

On examination, he was found to have a temperature of 102°; pulse of 140, and respiration, 36. The heart, lungs and abdomen were quite negative. There was a purulent mucus discharge in the posterior pharynx. The *neurological examination* showed all superficial reflexes to be absent. Positive Babinski on the left; a marked reflex of defense on the right, with a questionable Babinski. There was no paralysis of the extremities. Patellar reflexes were slightly increased. Kernig was doubtful.

The pupils were small and slightly irregular in outline, but the direct and consensual light reflex was present. It was impossible to test accommodation. The eye grounds were negative except for some increase in redness about the nerve head. There was no involvement of the eyelids or extrinsic muscles in so far as examination could be made.

The ears both showed retraction of the tympanic membrane.

The left membrane apparently had been perforated at some time previously. There was no discharge and no evident mastoid involvement.

Anteroposterior stereoroentgen-ray films and lateral films showed the outline of all the sinuses. They all apparently contained air.

The sphenoid especially showed a definitely thickened lining membrane. They did not suggest a sinus empyema as was noted later. The patient became restless and moaned most of the time. The temperature gradually increased to 109° F., before death on the third day.

The catheterized urine examination was negative. The blood count showed white blood cells 17,950; polynuclears, 85 per cent; large lymphocytes, 4 per cent; small lymphocytes, 5 per cent; large mononuclears, 2 per cent; transitionals, 4 per cent.

The blood Wassermann was negative. The spinal fluid was clear, flowed freely, cells and globulin were not increased. Wassermann and mastic reactions were normal.

Autopsy. Autopsy showed that the dura was quite firmly adherent over the vertex and base of the skull. The meninges were markedly congested. All the small vessels over the convolutions were filled with bright blood. All the veins were engorged with dark blood.

When the membranes were removed from the bone over the mastoid cells a dark discoloration of the bone was noted. There was no marked local meningeal reaction in these areas. The inner table of bone in these parts was easily removed with the point of a knife, opening the mastoid cells. They were voluminous on both sides. The uppermost cells on both sides were filled with a thin reddish fluid. The venous sinuses were not thrombosed.

The sphenoid and both ethmoids were filled with a foul, thick pus. The lining membranes of the cells were much thickened, and darkly colored, due to changed blood. There was no gross evidence of any direct path of infection between the sphenoid, ethmoids and meninges.

The right lung showed some old healed tubercles at the apex. Except for congestion, the heart, liver, kidneys, pancreas, spleen, stomach and intestines were negative.

At *autopsy* the brain appeared markedly congested, the small arteries over the convolutions being filled with bright red blood and the veins engorged by dark blood. The basal bloodvessels were rather small and showed some slight thickened patches.

The pia-arachnoid was rust-stained over the frontal poles. Small punctate softenings were seen in both globi pallidi.

The left hemisphere of the cerebellum was considerably smaller than the right.

Microscopically, the pia-arachnoid showed no increase in width in general, but in many areas, notably in the cerebellum and right Ammon's horn, hemorrhage had taken place, spreading the tissues. In the Ammon's horn the hemorrhage had already begun to organize, showing proliferating fibroblasts, also large numbers of polyblasts were present. The adjacent edges of the cortex had been invaded by the hemorrhages in several places.

All bloodvessels were excessively engorged with blood to such an extent that the cortical architecture was much disarranged. The adventitial coats showed no alteration but the elastic was slightly swollen. The endothelial cells of the vessels showed very active proliferation, many mitoses being seen and the cells were excessively swollen. Diapedesis was constant in all sections, but larger masses of blood, real hemorrhages, were also seen to a slight extent in the cortex, but more marked in the medulla and the globus pallidus of each side. In the medulla several vessels were seen in which the adventitial lymph spaces were packed with small lymphocytes and polyblasts, but no plasma cells were observed.

In both the right and left globus pallidus vessels were seen with a moderate amount of infiltration by small lymphocytes and mast-cells. Most noticeable of all was the very active proliferation of adventitial tissue around the vessels where constant mitoses were seen in great numbers. Several foci were seen in both nuclei where a vessel was surrounded by large masses of polynuclear leukocytes invading the tissue in all directions. Many degenerated foci were seen, some recent, showing hemorrhage with the beginning of phagocytosis and others older, some almost devoid of all cellular elements, others were packed with small phagocytes containing fat (granular cells) and still others where granular cells were present, but glia and connective tissue predominated. The left lenticular showed the same conditions as seen in the pallidi. Granular cells were scattered throughout all portions of the sections examined, both near and at a distance from vessels. These were frequently seen dividing both mitotically and amitotically and were probably both mesodermic and gliogenous in origin.

The nerve cells of the cortex were practically all in the first stages of dissolution of the protoplasm. Their bodies were finely granular and pale. The nucleoli showed invariably a splitting up of their substance into three or more bodies, frequently arranged in a row or in star form (a process considered by the Spanish school to be an attempt at proliferation by mitoses). There was some excess of satellitosis in the cortex, but it was not at all marked. There was also some proliferation of glia cells where hemorrhage had invaded the cortical margin and especially when organization had already begun in the hemorrhage. This condition was specially notable in the cerebellum.

Pathological Diagnosis. Acute purulent mastoiditis; old healed tubercles of lung; congestion of body organs; cerebral congestion; localized meningeal hemorrhages; acute proliferative changes in cerebral vessels; multiple cortical hemorrhages; multiple focal encephalitic lesions, chiefly in the basal ganglia; severe degenerative changes in cortical nerve cells; histopathological process of lethargic encephalitis.

DIFFERENTIAL CLINICAL DIAGNOSIS.

In the group of cases we have presented the following disease entities must be considered: Meningo-encephalitis lethargica, tuberculosis, meningo-encephalitis, syphilis of the central nervous system, tetanus, streptococcic meningo-encephalitis and chorea insaniens. In addition to these conditions acute cerebral manifestations are seen in botulismus, cerebral tumor, typhoid fever, acute delirium in hysteria, trypanosomiasis, uremia, anterior poliomyelitis, and epidemic cerebrospinal meningitis.

Botulismus usually is associated with a definite history of food poisoning, with severe acute gastrointestinal symptoms together with some cerebrolulbar symptoms. The infective agent may be discovered and the clinical course of the disease is usually afebrile.

Typhoid is usually eliminated by the physical and laboratory findings common in typhoid fever.

Cerebral tumor has been misjudged oftentimes during the last pandemic, especially in the rare case where the cardinal symptoms of headache and intracranial pressure as shown in the fundus were absent. A careful anamnesis, neurological examination, and, as a rule, negative laboratory findings, together with a few days' observation, will usually suffice to make differentiation possible.

Acute delirium usually gives only the delirium, unassociated with fever, abnormal laboratory findings, or neurological disturbances.

Chorea insaniens may present difficult problems, as witnessed in one of our patients. With the evidence of an acute streptococcic infection or the common lesions produced by such an infection, as endocarditis, the diagnosis is suggested. Numerous observations of choreiform movements have been recorded in patients diagnosed as lethargic encephalitis. The question is justly raised in consideration of our case, whether one should consider that there is a choreiform type of encephalitis lethargica. The movements produced by cerebral irritation or by stimulation are not necessarily due to one type of infection. Further, the cases of this type present a most difficult problem, for in our patient who had a violent agitation, and the postmortem finding of acute friable vegetations on the mitral valves, Dr. Gurd has found so many histopathological changes that the brain specimen cannot be classified separately from the brains of characteristic encephalitis lethargica.

Hysteria is usually apyrexia. We must rely largely on the stigmata: sensory disorders, contracted visual fields, anesthetics, and the unchanged reflexes and negative laboratory examinations.

Trypanosomiasis has presented interesting similarity in the pathological brain findings, but fortunately we are seldom called upon to make a clinical differentiation.

Uremia will usually be excluded by: (1) Urine examination; (2) blood-pressure; (3) blood chemistry; (4) increased incoagulable

nitrogen in the spinal fluid as shown by direct Nesslerization, and (5) the absence of any definite evidence of infection as shown by fever. In one of our patients typical encephalitis lethargica was complicated by a chronic nephritis with moderate hypertension.

Epidemic cerebrospinal meningitis gives a cloudy spinal fluid, containing large numbers of pus cells with intracellular diplococci. Further, as a rule, the stormy onset with fever and acute severe meningospinal symptoms, as head pains, stiff neck, opisthotonus, rigidity and Kernig's signs, together with the eye and neurological findings are sufficient to obviate difficulty in the differential diagnosis.

Anterior poliomyelitis, when the meningo-encephalitic complex is prominent, presents difficulties which are confusing, whereas in the presence of selective paralysis of the extremities the diagnosis would be more evident. The stormy onset, with marked fever, oftentimes vomiting, severe headaches, meningeal symptoms, associated with early evidence of true motor paralysis, is more characteristic of this condition. The spinal fluid examination will differentiate this condition from meningococcus infection and acute syphilis.

Our cases deal more specifically with tetanus, tuberculosis, syphilis and acute encephalitis, both of the lethargic and streptococcic types.

Tetanus under the conditions of one of our patients did not present the classical syndrome. Except for the tetanic contraction of the masseter muscles, the case might clinically have belonged to other encephalitic diseases. The serological examination of the spinal fluid, together with the low globulin content is against syphilis; on the other hand the white cell count of both the spinal fluid and blood is in favor either of tetanus or tuberculosis, however, in our cases tuberculosis always gave a very marked globulin reaction. Our patient probably had a cephalic type of tetanus, but without the evidence of a portal of entry we feel that, in the absence of the finding of tubercle bacilli in the spinal fluid, a positive differential diagnosis could not be made between tuberculosis and tetanus without the *micropathological study* of the brain. The marked pleocytosis in the spinal fluid is a definite argument against encephalitis lethargica. Further, the complete lack of involvement of the nerves of the eyes is most unusual in lethargic meningo-encephalitis.

Tuberculous meningo-encephalitis may present a mixed complex, varying on the extent and locating of the brain lesions. That the disease is a true encephalitis, especially in adults, is evidenced by the fact of the marked pathological reaction and the finding of the bacilli within the encephalon. As a rule, the meningeal involvement is more marked than is seen in encephalitis lethargica. This probably accounts for the greater severity of the headache. Tuberculosis, as a rule, gives bizarre colloidal reactions, whereas syphilis gives definite reactions together with specific complement-fixation.

Streptococcic encephalitis may occur and show minimal meningeal involvement. This accounts for the negative spinal fluid as found in Cases IX and XI, although the brain sections showed extensive changes. An infected wound, a streptococcic sore throat, or an infected accessory or mastoid sinus would suggest this type of encephalitis.

Acute syphilis is polymorphous in its manifestations and must, as a rule, be diagnosed by the much increased cell count of the spinal fluid, marked globulin increase, colloidal reactions and the specific complement-fixation tests.

Lethargic meningo-encephalitis, to us, in spite of the many so-called forms described in the recent voluminous literature, presents a fairly definite clinical complex. It has oftentimes been said that the condition must be diagnosed by a *process of elimination*, yet a considerable confusion is existing because the disease presents many phases, and some of the cases reported as such have not had the proper *laboratory* and *clinical tests*, and most of all, the *histopathological* confirmation. The basis of classification of clinical manifestations is confusing because many signs may be presented depending upon the location of the pathological reaction. However, when the whole clinical picture is obtained, there is, as a rule, a fairly constant clinical entity. The combination of *fatigue*, *lethargy*, *headache*, *giddiness*, *visual disturbances* of which *diplopia* is most common, together with *fever*, *progressive weakness*, *mental dulness*, *radicular pains*, and definite *neurological findings* is not usually seen in other conditions. These taken together with *slight increase* in the *white blood cells*, and *spinal fluid examination* give a definite picture. In our experience the spinal fluid has always been slightly changed. The cells have varied from 20 to 80. The globulin has always been present in a trace and there have been slight colloidal changes. Two factors influence the cell count in this condition, namely, the age of the fluid, and the apparent stage of the disease. In a number of cases where spinal drainage was done for therapeutic reasons, the cell count progressively decreased. The spinal fluid has an increased volume as shown by the frequently repeated drainage and also at postmortem.

We do not wish to present a lengthy résumé of the various findings in encephalitis lethargica because recent literature contains many excellent reviews. The clinical diagnosis must of necessity be made with most assurance when the composite picture is presented of history, physical examination, blood and spinal fluid, and urine examination. In our experience the spinal fluid showed the most consistent changes. Unfortunately the amount of glucose was not determined in our cases. Dopter and Netter, as quoted by Benard¹ consider that "l'hyperglycorachie" is a very important finding in encephalitis lethargica: Benard says, however, that increases are found in diabetes, uremia, bronchial pneumonia, Malta fever, rabies,

pertussis and cerebral tumor, and the increase in acute encephalitis should be considered merely as additional evidence. It probably indicates that the "centre de la glycogenese est touché." This examination is of importance in the differentiation of the lethargic types from tuberculosis. We have found, as Netter states,² that there is a tendency for the pleocytosis of encephalitis lethargica to change as the disease progresses. The cell count is usually higher in the earlier stages of the disease. In reviewing the reported cases and in studying the patients we have seen, it seems to us that the spinal fluid changes are quite constant in encephalitis lethargica, and further that a differential diagnosis is not warranted without this laboratory data. In the differentiation from tuberculosis, Netter² has stated the lymphocytosis is not infrequent in encephalitis lethargica, but is less than occurs in tubercular meningitis.

The Wassermann fixation and the colloidal chemical reactions serve best to differentiate tuberculosis from the various syphilitic diseases. Leukocytosis is quite common in tuberculous meningo-encephalitis, rare in syphilis and very moderate in encephalitis lethargica.

There has been considerable discussion concerning the serological reactions in encephalitis lethargica, especially the colloidal reactions: Recently a patient, who had a well-developed Parkinson syndrome, was studied in consultation with Dr. Charles McVey, by one of us (Gilbert). The patient had residuals of eye muscle involvement, especially of the pupil, with a history of what was undoubtedly an acute encephalitis of a year past. The blood Wassermann showed a very slight complement-fixation, while the spinal fluid showed an increase of a few cells, a slight trace of globulin (Pandy), a three plus complement-fixation with human-heart-cholesterinized antigen, using 0.8 cc of spinal fluid and a colloidal-gold reaction of 2455431000 and mastic of 121000000. Subsequent antiluetic treatment had no effect on the patient's condition. Leavitt³ reported a case of paralysis agitans type of lethargic encephalitis that showed a positive Wassermann reaction on the spinal fluid, a cell count of 22, a positive globulin reaction and a colloidal gold curve of 3455432110. The blood Wassermann was negative. The patient had severe bodily pains, incontinence of urine and feces. The pain was followed in three weeks by tremors and speech changes. The condition of the patient became progressively worse under antiluetic treatment.

The serological changes which we have mentioned in the two preceding cases are of marked interest in relationship to some of the specific pathological changes noted by Dr. Gurd in the brains of patients dying of encephalitis lethargica. It has been observed that there is constantly a marked fatty change in the endothelial cells about the foci as seen in the brain sections. In view of the fact that these changes are most marked about the small veins and in the lumen of the same, it would be logical to suppose that in the later

stages of this condition there may be definite lipoidal changes which might reasonably be supposed to affect the serological reactions of the spinal fluid and possibly also that of the blood.

CHART I.—BLOOD EXAMINATION.

Case.	White blood cells.	Polymorphonuclears.	Eosinophiles.	Basophiles.	Large leukocytes.	Small leukocytes.	Large mononuclears.	Transitionals.	Wassermann.	Blood nitrogen, gm. per 100 cc.
I	13,000	73	0	0	10	7	6	4	Neg.	0.042
II	10,000	75	0	0	5	11	5	4	Neg.	
III	16,500	Neg.	
IV	15,450	89	0	0	4	2	5	0	++++	
V	10,000	80	0	0	2	10	4	4	Neg.	
VI	12,000	68	0	0	12	14	4	2	Neg.	
VII	9,000	86	1	0	1	11	1	0	Neg.	
VIII	13,250	70	0	0	10	12	6	2	Neg.	
IX	16,000	78	0	1	9	8	3	1	Neg.	*
X	8,000	++++	
	31,000	85	0	0	5	6	2	2	..	
XI	17,950	85	0	0	4	5	2	4	Neg.	

* Coincident with otitis media.

CHART II.—SPINAL FLUID EXAMINATION.

Case.	Char-acter.	Pressure.	Cells.	Globulin.	Wasser-mann.	Mastic.	Clinical diagnosis.
I	Clear	+	260	++++	+	221100	} Tuberculous meningo-encephalitis.
	Clear	+	200	++++	+++	211000	
II	Clear	+	50	Trace	Neg.	} 110000	} Lethargic meningo-encephalitis.
	Clear	+	20	++	Neg.		
III	Clear	1	300	+	Neg.	110000	Tetanus or tuberculous meningitis.
IV	Clear	+	150	++++	Neg.	111000	Tuberculous meningo-encephalitis.
V	Clear	+	80	Trace	Neg.	111100	Lethargic meningo-encephalitis.
VI	Clear	+	21	Trace	Neg.	110000	Lethargic meningo-encephalitis.
VII	Clear	++	400	++++	Neg.	} 211110	} Tuberculous meningitis.
	Clear	++	450	++++	Neg.		
	Clear	++	250	++++	Neg.		
VIII	Clear	+	30	Trace	Neg.	111000	Lethargic meningo-encephalitis.
IX	Clear	1	3	0	Neg.	000000	Streptococcus encephalitis.
X	Clear	+	40	++++	++++	444432100	Acute paresis; otitis media.
XI	Clear	0	3	0	0	0	Streptococcus encephalitis; lethargic meningo-encephalitis.

The Histopathological Résumé. The *pathology* of the cerebrospinal nervous system so far as studied in the eleven cases here presented falls readily into several distinct groups.

In Cases I, IV and VII, a typical picture of tubercular meningo-encephalitis is offered. Although the cases vary in some details the following phenomena are common to all: Macroscopically severe leptomeningitis, internal hydrocephalus and cystic choroid plexes.

Microscopically tubercle bacilli were found in greater or lesser numbers in each case, the meningitis was characterized by the presence of lymphocytes, plasma cells, giant-cells, polyblastic granular cells, but especially by the presence of large numbers of large pale giant phagocytes. The inflammatory process had invaded the choroid plexus to a greater or lesser extent in each case and also the ependyma of the ventricles. Case VII, in which the internal hydrocephalus was less marked than in the other two cases also showed less involvement of the ependyma by the inflammatory process.

Many bloodvessels showed swelling and loosening of the endothelial lining which was frequently seen floating in the vessel lumen attached only at one point.

In each case considerable involvement of the nervous tissues had taken place by the extension of the inflammatory infiltration along the course of the vessels entering from the pia. This involvement was always more marked at the base of the brain and in addition small inflammatory foci were seen scattered irregularly in the medulla, pons, peduncles and basal ganglia, but in Cases I and IV particularly noted in the nuclei of the third nerves.

The nerve cells were more or less injured in accordance with their proximity or remoteness from the inflammatory process.

Glia reaction was very marked in all areas where the meningitis was present and varied with the severity of the meningitis process and the presence of the inflammatory foci.

Cases II, V, VI, VIII and IX present the more or less typical findings of acute (to some extent) chronic meningo-encephalitis occurring with the syndrome termed lethargic encephalitis.

All the nervous structures showed extreme edema both macro- and microscopically. In most of the cases the brains were of a cherry-red on autopsy.

The meningitis was always very slight and only seen in patches. Hemorrhage in the meninges was present, and in some of the cases but not invariably, very small hemorrhages and diapedesis, mostly in the basal ganglia, pons, peduncles and medulla. The meningitis consisted of an infiltration of very slight density by lymphocytes and occasional plasma cells.

No inflammatory foci were seen in the cortex. Inflammatory foci were observed with very irregular distribution in the basal

ganglia, pons, peduncles and medulla. These foci have as a basis, preferably the veins, although in some of the cases an artery would be seen involved. Fatty degeneration of the cells in a focus was frequently seen and in one case severe fatty degeneration of the capillaries. The foci were composed of polyblasts, lymphocytes and plasma cells. No plasma-celled infiltration of the cortical capillaries was observed, but plasma-cell infiltration of the capillaries in the localities near foci, as in the pons, peduncles, etc., was very general and widespread. A very marked feature in all of the cases was the swelling and active proliferation of the endothelial cells of the bloodvessels with its frequent desquamation sometimes to such an extent that it blocked the vessels. Polynuclear leukocytes were frequently present in large numbers in the lumina of the vessels.

Nerve-cell injury was very variable and in general of the character and extent which is caused by severe edema.

Glial reaction was extremely limited except in those cases in which older foci of degeneration were seen.

Case III was extremely interesting from its negative diagnostic value as meningo-encephalitis tuberculosa and meningo-encephalitis lethargica could be absolutely excluded, whereas the picture of severe degeneration of the nerve cells without axonal reactions and the progressive and regressive changes in the glial structure is that seen in tetanus.

Case X offered a very characteristic picture of severe general paralysis of the insane, probably rather acute in character; moderate to severe generalized leptomeningitis with plasma cells in the majority in the infiltrate with a compliment of small lymphocytes, a few polyblasts and many mast-cells, no large phagocytes or giant-cells. There was generalized infiltration by plasma cells of the capillaries in all parts of the brain studied. There was much increase in all glial elements and many rod cells were present.

The fact that the cytological architectonic of the cortex was not altered and that the degeneration of the nerve cells was more moderate in character than usual in general paralysis of the insane was probably due to the acuteness of the attack and its limited duration of time.

Case II stood alone pathologically, the most marked feature being the very severe degenerative and the marked regenerative processes in the bloodvessels, the degeneration leading to hemorrhages and softening of the tissues, and the regeneration to a great excess of connective tissue around the bloodvessels. In addition, a direct invasion of the tissues of the lenticular nuclei by polynuclear leukocytes, the whole giving the picture of encephalitis of the basal ganglia, probably of streptococcic origin. The absence of purulent meningitis, which might have been anticipated in this case, is notable.

Summary. From this brief study can one draw any conclusions as to the variety of encephalitis or meningo-encephalitis from

the localizing symptoms present? That question must be answered in the negative, since localization of the foci in the 3 cases of tubercular meningo-encephalitis, where practically all the nuclear areas in the basal ganglia and the central gray matter about the aqueduct, etc., showed foci in much the same location and extent as those seen in the cases of lethargic encephalitis. The same holds true for the presence of tremors, choreiform movements, etc., as in all the cases of encephalitis studied here included Cases I, II, IV, V, VI, VII, VIII, IX, and XI, foci of inflammation or degeneration were seen so widely, diffusely and irregularly scattered that no conclusions as to localization of symptoms could be drawn.

The important question still remains: Are there definite pathological pictures of the various forms of meningo-encephalitis?

Tubercular meningo-encephalitis may be cited affirmatively as even in the absence of tubercle bacilli, which are not always easy to demonstrate, the severe meningitis with plasma cells, small lymphocytes, giant-cells, but more especially the predominance of giant phagocytes renders a diagnosis easy.

General paralysis of the insane with a more or less severe meningitis with plasma cells, mast-cells, lymphocytes, the absence or rare appearance of giant phagocytes, the presence of generalized plasma-cell infiltration of practically all the capillaries in the cortex of a brain area, and the presence of large numbers of rod cells renders a diagnosis easy.

Left for consideration, then, is lethargic meningo-encephalitis. In acute cases certain points stand out: The involvement of the veins in the inflammatory process, to the exclusion of the arteries; the very slight connective-tissue reaction or its complete absence; the presence of fat in the cells of the foci and in the vessel endothelial cells and the minimal amount of reaction in the glia. The cases here reported illustrate these points. But in cases of more chronic character or cases dying months or years after the acute process has ceased, the above diagnostic points are bound to disappear. This is shown by the old foci seen in some of these cases where, with their increase in connective-tissue and glial tissue, they are indistinguishable from encephalitic foci of many other origins. The importance then of most careful *clinical, serological, bacteriological* and *pathological* study of all available cases cannot be too strongly urged for the purpose of obtaining clearer views of *etiology, pathology, symptomatology, course* and *prognosis*, immediate and remote, of the disease, with the ultimate goal of its *prevention* and *treatment*.

BIBLIOGRAPHY.

1. Benard, R.: Paris méd. ann., 1920, 10, 474.
2. Netter: Bull. Acad. de méd., 1920, 83, 109; Bull. et mém. Soc. méd. d. hôp. de Paris, 1920, 44, 98.
3. Leavitt: Arch. Neurol. and Psychiat., 1921, 5, 99.

THE ACCURACY OF THE CAT METHOD FOR THE ASSAY OF DIGITALIS.

BY CHARLES C. HASKELL, M.D.,

AND

R. H. COURTNEY, M.D.,

RICHMOND, VA.

(From the Laboratory of Pharmacology, Medical College of Virginia.)

DURING the winter of 1916 and the early spring of 1917, a number of tinctures, made from digitalis leaf, grown in the vicinity of Richmond by Mr. J. W. Wilber were assayed in our laboratory by the one-hour cat method of Hatcher and Brody. On account of the unusual potency of these samples, they were kept in order to determine the effect of age; and in 1922, they were retested by the cat method. The results which were obtained on this second assay appeared to indicate that certain of the tinctures had deteriorated; while others retained their strength unaltered. This was indeed surprising, in view of the fact that the samples were originally of approximately the same strength; were all made from the same variety of leaf; and had been extracted and preserved in the same manner. Further investigations, carried out not only on these samples but on other tinctures and on solutions of ouabain have convinced us that the apparent deterioration of the original samples may be explained by the recognition of imperfections in the method of assay as applied by us. In order to make this clear, it will be necessary to give the details of our tests.

In carrying out the assays by the cat method, the technic described by Hatcher and Brody has been followed with only slight modifications. Only full grown, apparently healthy cats have been used; and lactating and pregnant females have been eliminated where the amount of digitalis required to cause death has differed from the average for that particular sample. In most cases, ether has been used for anesthesia; occasionally, chlorotone has been given orally or intraperitoneally. In a few cases, the combined method, making use of ouabain, was employed; generally, the diluted tincture alone was slowly injected until death occurred. The rate of injection was about 0.5 cc every minute.

From the results of the assays, the tests may be placed in three classes: First, those in which the cats showed no marked individual variations in their resistance; second, where, in spite of decided individual differences, the averages of the different series agreed closely; and, third, where repeated tests gave discordant figures.

As illustrative of the first class, sample No. 36 may be cited. This sample was first tested in February, 1917; only two cats being

used; the lethal doses were 41.5 and 43.0 mg. per kg. respectively. In May, 1922, the sample was again assayed; three cats being used, and the lethal doses were found to be 43.63, 41.2 and 42.07 mg. per kg. respectively. The difference between the smallest and the largest dose is seen to be less than 6 per cent; while the averages of the two series check almost exactly (42.25 and 42.3).

In discussing the technic of the cat method, Eggleston has said: "It is, therefore, obvious that one must not trust the reaction of a single animal. . . . In carrying out the cat method of standardization in actual practice, at least three animals are used, and if all three give closely similar results, the average is taken as being correct. If two of the results are quite close, but the third is considerably at variance, a fourth or even a fifth test is made before an average is struck."

Moreover, before calculating the average for a series, this author states, with justice, that obviously abnormal animals should be eliminated. It has been our experience that, following these directions, it is often possible to secure concordant results in the face of considerable individual variation of the animals used. This is shown in Table I, containing a summary of the different assays of sample No. 39.

TABLE I.—DIFFERENT ASSAYS OF TINCTURE NO. 39 BY CAT METHOD.

Date of assay.	Lethal dose, mg. x kg.	Average.
Feb. 3, 1917	68.6	71.25
3, 1917	65.2	
14, 1917	77.8	
14, 1917	73.4	
Jan. 24, 1921	79.2	72.00
24, 1921	67.5	
27, 1921	69.3	
27, 1921	102.0*	

One would infer that the fourth cat used in 1921 was abnormal in reaction; after eliminating this animal, in spite of a not inconsiderable difference among the individuals of the two series, the averages agree within less than 2 per cent.

Unfortunately, with us, it has not always been possible to secure such happy results. Thus, in assaying sample No. 34, two cats were used on March 10, 1917; the doses required being 54 and 40 mg. per kg. respectively. Four days later, two more cats were used; the doses necessary at this second assay were 72 and 70 mg. per kg. On March 16, another pair of cats gave figures of 62.2 and 66.7 mg. per kg. respectively. The second and third pairs gave averages differing by about 9 per cent; while the larger dose of the first pair differs more than 23 per cent from the average of the second pair. But still more disappointing results were secured when

* The averages are calculated after eliminating this experiment.

this sample was tested in 1922 and 1923. These results are given in Table II.

TABLE II.—ASSAYS OF TINCTURE NO. 34 BY CAT METHOD.

Date of assay.	Lethal dose, mg. x kg.	Average.
June 15, 1922	41.1	64.23
15, 1922	62.3	
15, 1922	89.3	
19, 1922	104.7	
19, 1922	99.4	
Feb. 10, 1923	80.0	82.36
10, 1923	87.8	
10, 1923	112.8*	
10, 1923	79.3	
26, 1923	101.0*	86.75
26, 1923	86.0	
26, 1923	96.9*	
26, 1923	87.5	
Mar. 28, 1923	62.2	68.25
28, 1923	74.3	
29, 1923	58.2	62.30
29, 1923	66.4	
29, 1923	105.6*	

The average of the three pairs of cats used in 1917 was 60.8 mg. per 1 kg. The three cats used on June 15, 1922, gave an average not far from that of the initial assays; but three days later a pair of cats gave the fairly closely checking figures of 104.7 and 99.4 mg. per 1 kg. Of the four cats used on February 10, 1923, one would infer that number three was abnormal; after its elimination, an average of 82.36 is obtained. Sixteen days later, serious difficulties are encountered. Of the four cats used on that date, which are "abnormal"? Two check quite closely at 86.0 and 87.5; while two others give values of 101 and 96.9, neither one of which differs more than 2 per cent from their average. However, if we accept the two smaller figures, an average of 86.75 is secured; agreeing fairly well with the assay carried out earlier in this month and indicating a definite loss in the strength of the tincture. On March 28, however, the two cats used appear to show that the tincture is regaining its strength, and this is apparently confirmed by the tests carried out the following day, if we eliminate the supposedly abnormal cat that required 105.6 mg. per 1 kg. to cause its death.

Eggleston¹ has recognized the chance of two cats in the same series being "abnormal" in a similar direction, but he considers this

* The averages are calculated after eliminating these experiments.

¹ Biological Standardization of the Digitalis Bodies by the Cat Method of Hatcher, *Am. Jour. Pharm.*, 1913, 85, 99.

“an almost impossible accident.” As has been pointed out, this actually occurred in the tests of No. 34 on February 10, 1923, and our records show that a similar accident has occurred in the assay of other samples. These instances have been collected and placed in Table III. It is to be understood that, in most cases, a much larger number of cats were used in each assay; we have selected only the ones illustrating our point.

TABLE III.—ASSAYS SHOWING CHECKS AT DIFFERENT FIGURES.

No. of sample.	Lethal dose, mg. x kg.	Total number of cats used.
9	$\left\{ \begin{array}{c} 47.8 \\ 48.0 \\ 82.0 \\ 86.0 \end{array} \right\}$	13
11	$\left\{ \begin{array}{c} 62.8 \\ 67.0 \\ 102.6 \\ 127.7 \end{array} \right\}$	12
33	$\left\{ \begin{array}{c} 61.5 \\ 61.6 \\ 87.1 \\ 87.7 \end{array} \right\}$	6
45	$\left\{ \begin{array}{c} 60.5 \\ 61.3 \\ 81.6 \\ 81.7 \end{array} \right\}$	9
47	$\left\{ \begin{array}{c} 28.2 \\ 26.8 \\ 48.5 \\ 49.7 \\ 60.3 \\ 60.6 \\ 60.7 \\ 61.0 \\ 67.0 \\ 67.8 \\ 72.0 \\ 72.7 \\ 81.5 \\ 81.6 \\ 92.3 \\ 92.5 \end{array} \right\}$	36
60	$\left\{ \begin{array}{c} 46.0 \\ 47.0 \\ 56.6 \\ 57.8 \end{array} \right\}$	6

In justice to the method, attention must be called to the fact that in most cases, these “abnormal” pairs did not come in the order in which they are placed in the table; they were usually separated by results closer to the average. Nevertheless, they did occur; in some instances, in such order as to lead to the most erroneous deductions.

To what are these undesirable results attributable? Hatcher and Brody² have called attention to the fact that certain tinctures show considerable precipitation on dilution with saline. This could scarcely explain our results, since the same procedure was followed in each assay, and precipitation, if it exerted any influence, should have led to a constant error. Furthermore, no decided difference could be observed when the "combined method" of assay was resorted to.

Sex, apparently, does not affect the reaction of cats to digitalis. This is illustrated by the figures in Table IV, where the averages for those samples assayed on at least two cats of both sex are given.

TABLE IV.

No. of sample.	Assay on male cats,		Assay on female cats,	
	mg. leaf x kg. cat.		mg. leaf x kg. cat.	
9	65.68		60.45	
11	68.26		65.94	
33	64.10		62.32	
34	71.76		74.48	
36	42.30		43.97	
39	70.46		75.40	
42	58.70		67.86	
43	60.40		68.63	
45	73.25		73.00	
47	62.44		65.94	
52	66.06		62.74	
S.-P.	54.30		43.50	

Eggleston has shown that season may affect the resistance of cats to digitalis poisoning. According to this author, greatest individual variability is to be encountered in the hot months of July and August, but, while we are able to confirm his observation as to variability of cats at this time of the year, we have not found that such differences occur exclusively in the summer months, as may be seen by reference to the figures for the February and March assays of No. 34 (Table II).

Conclusions. It is not our desire to create the impression that the cat method of assay is valueless; on the contrary, it is our personal opinion that it excels other methods for the physiological standardization of digitalis. The impression that appears to prevail in some quarters is that two or even a single cat suffices to determine with extreme accuracy the strength of a digitalis preparation, and this in spite of the definite statements to the contrary made by Eggleston. Our own observations offer additional evidence that only by the use of large numbers of cats can this accuracy of standardization be attained and, naturally, cast some doubt on the statements that have been made regarding deterioration of tincture of digitalis as judged by the cat method of assay.

² Biological Standardization of Drugs, Am. Jour. Pharm., 1910, 82, 360.

PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF A
CASE LASTING ONE HUNDRED AND FIFTY-THREE
HOURS WITH RECOVERY.

BY WILLIAM B. PORTER, M.D.,

ROANOKE, VA.

THE prognostic significance of paroxysmal ventricular tachycardia makes its recognition of definite importance. Judging from the small number of cases reported, seemingly it is one of the rarest disturbances of cardiac mechanism. Its differentiation from paroxysmal auricular tachycardia is important and will become more universal because of the increased use of the electrocardiograph.

The case here presented is of prime interest in that it again emphasizes the association of paroxysmal ventricular tachycardia with grave myocardial disease; in that the patient survived an attack of unusual duration; and in that the electrocardiograms showed independent auricular activity with unusual clearness.

Case Report. W. T. W., a white male, aged forty-six years, was admitted to the medical division of the Lewis-Gale Hospital, December 12, 1922, complaining of shortness of breath, chiefly nocturnal, precordial pain, and swelling of the lower extremities and abdomen. He stated that his illness began on May 5, 1922, when he was awakened by violent pain in his chest which radiated to both arms, especially the left arm. His family physician who was with him stated that no relief being obtained from hypodermics of morphin, chloroform was administered. The attack lasted for eight hours, during which period cyanosis was marked, and the patient presented many aspects of impending death. Since that time the patient has been unable to attend to any of his duties as a minister because even moderate exertion brought on recurring attacks of angina and dyspnea. One month before the onset of his illness his blood-pressure was 160-90.

Previous History. The patient gave a history of having had measles, mumps and pneumonia, and one year previously influenza. With the attack of influenza there was an infection of the left maxillary sinus. This was drained and was cured. He had frequent attacks of migraine prior to the original attack of angina but since then had been free from headache.

Physical Examination. The physical examination showed slight cyanosis with moderate respiratory distress. There was distinct venous distention in the neck. The heart was definitely enlarged, with a transverse diameter of 19 cm. No murmurs were heard. The cardiac rate was 98. Aortic dulness was increased. The systolic blood-pressure was 122, the diastolic blood-pressure was 100.

Moist rales were heard in bases of both lungs. The liver was 6 cm. below the costal margin in mid-clavicular line and there was marked tenderness over it. There was slight ascites with considerable edema over the sacral area and lower extremities.

Laboratory Examination. Examination of blood and urine showed nothing of importance. Wassermann reaction, negative; blood urea, 41 mg. per 100 cc.

Roentgen-ray of chest, 7-foot plate: Transverse diameter of chest, $31\frac{1}{2}$ cm.; heart, 19 cm.; aorta, 9 cm.

Electrocardiograms: Fig. 1 showed ventricular complexes of a distinctly abnormal type. There is a slight widening of the *QRS* complexes, isoelectric *T* wave in Lead II, notching of *P* wave in Leads I and II.

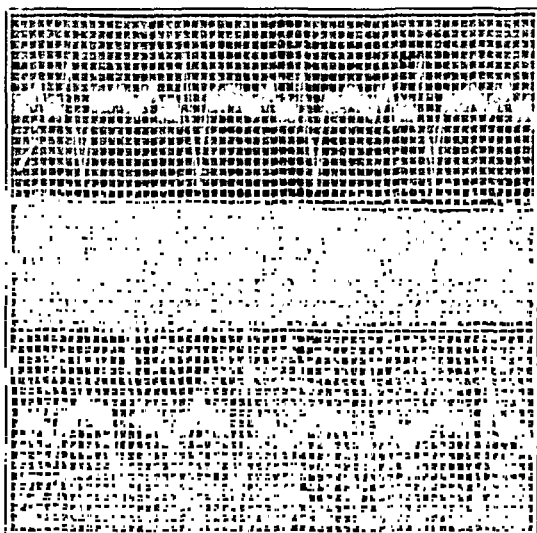


FIG. 1.—Taken December 14. No disturbance in rhythm is noted.

Course in Hospital. The patient remained in the hospital for four weeks during which time his clinical condition improved. The edema lessened and many of the signs of congestive heart failure disappeared. During his stay in the hospital he had several mild attacks of angina, but none severe enough to require morphin for relief. The patient returned home, but on March 1, 1923, was readmitted to the hospital. At this time there was marked ascites and edema of the lower extremities and scrotum. The patient stated that he had been bedridden since leaving the hospital. He also stated that recently his abdomen had become markedly swollen and that paroxysmal palpitation had become very troublesome. On the day of his admission he began with one of his attacks of so-called palpitation.

Physical Findings. There was extensive edema of body, scrotum and extremities and the veins in the neck were full and pulsating.

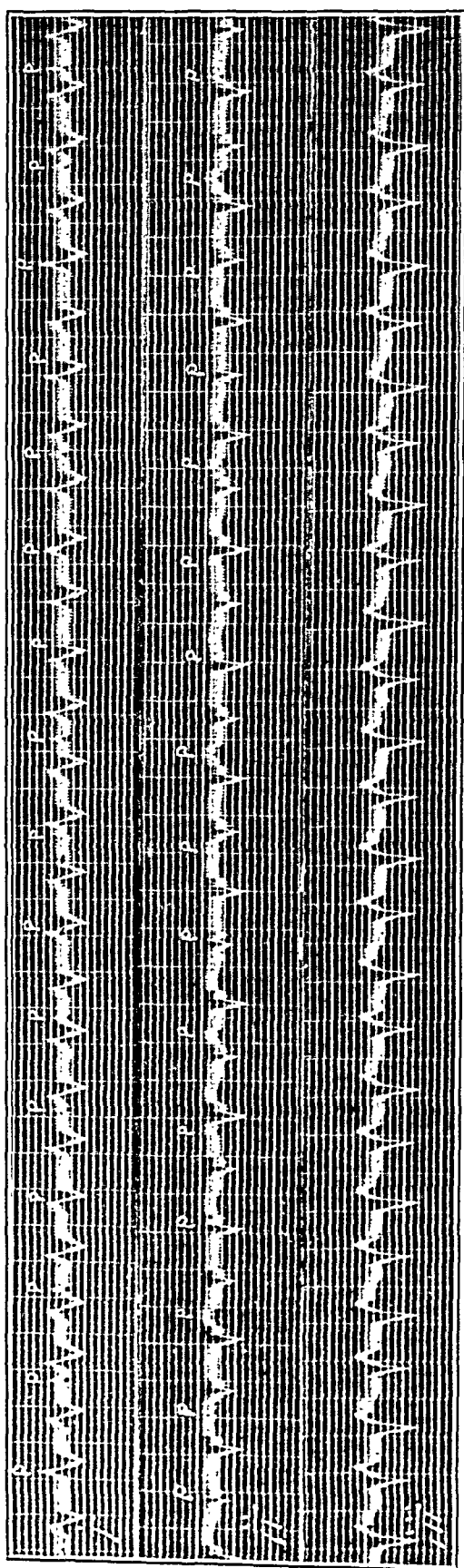


Fig. 2.—Taken March 2, 1923, on second day of the attack. Ventricular paroxysmal tachycardia. Auricular rate, 120; ventricular rate, 204.

The heart was markedly enlarged but because of existing body edema, borders could not be accurately demarcated. The cardiac rate was very rapid, 190 plus, and apparently regular. The pulse was small, compressible and arrhythmic. Blood-pressure was 80. The abdomen was markedly distended with ascitic fluid. The attack of tachycardia lasted until the evening of March 7, a period of six days and nine hours from the onset.

The electrocardiogram (Fig. 2) was taken on March 2. During the attack of tachycardia many tracings were made, but the one selected best illustrates the type of cardiac action observed.

Electrocardiogram: Ventricular paroxysmal tachycardia. An independent auricular activity is easily recognized in Leads I and II, rate 120; ventricular rate 204. There is a peculiar alternation of the ventricular complexes in all leads, especially marked in Leads II and III.

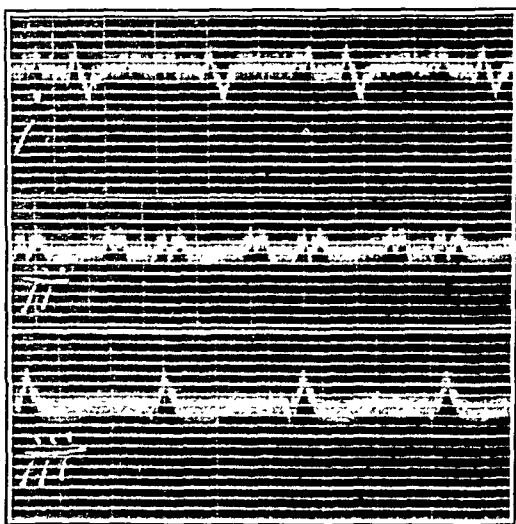


FIG. 3.—Taken March 9, 1923, two days after the cessation of the paroxysm.

On the second day after the cardiac mechanism had returned to normal there was aspirated from the peritoneal cavity 3000 cc of ascitic fluid.

An opportunity to make further electrocardiographical studies since March 9, 1923, (Fig. 3) which was the day after the cessation of the tachycardia, has not been afforded, but the patient has been observed in his home in several attacks of tachycardia, one lasting thirteen hours or more. Frequent extrasystoles, apparently of ventricular type, are noted daily. At this date the patient is in the terminal stages of cardiac failure.

Discussion. Robinson and Herrmann¹ have stressed the association of paroxysmal ventricular tachycardia with coronary occlusion. One of the cases reported by these observers had an attack lasting apparently eleven days, and lived for a few days after the cessation of the paroxysm.

The case here presented undoubtedly had a coronary thrombosis at the onset of the cardiac failure dating from the attack of prolonged and severe angina pectoris. From that date the patient was never able to regain sufficient cardiac reserve to enable him to "carry on" with any degree of efficiency or comfort. The clinical progress of the case was that of a progressive myocardial disease.

One is safe in inferring, from a study of the cases reported and from the evidence presented in the case here studied, that paroxysmal tachycardia of ventricular origin is invariably associated with advanced and grave myocardial disease.

The clinical recognition of any phenomenon either of cardinal diagnostic importance, or of positive prognostic significance is always desirable. Strong and Levine² emphasize the importance of ventricular irregularity as an aid in the bedside recognition of this disturbed mechanism. They point out the importance of prolonged auscultation in the recognition of this irregularity. Ventricular irregularity can be detected in most, if not all, of the tracings of the reported cases. It must be admitted, however, that while this irregularity is apparent on the cardiograms its auscultatory detection will be most difficult. With a rate of 190 or more the diastolic period is so markedly abbreviated that an irregularity of a degree capable of clinical recognition is not very probable.

Wolferth and McMillan,³ in a recent report of 4 cases, have reviewed the literature of the previously reported cases. They outlined the cardinal principles which should guide one in the recognition of paroxysmal ventricular tachycardia. The positive recognition of auricular activity occurring independently of, and at a slower rate than the complexes of ventricular origin; and of the ventricular complexes presenting distinctly abnormal form, is of supreme importance. The occurrence of isolated ectopic ventricular beats before or after the paroxysm is suggested as a guide to recognition. The case here presented possesses these hall-marks. The attacks occurred in paroxysms and were undoubtedly the cause of the paroxysmal palpitation. If this be true this patient had a large number of recurring paroxysms. Independent auricular activity is easily recognized in leads I and II of the electrocardiograms. The tracings show a perfect dissociation of auricular and ventricular activity, the auricles beating at an independent rate of 120, the ventricles beating at a rate of 204. Ectopic beats of ventricular origin were frequently observed though not recorded graphically.

The effect of prolonged ventricular activity on a heart already severely damaged by degenerative processes is of particular clinical interest. Barcroft, Boch and Roughton⁴ have studied the circulatory condition existing in a state of paroxysmal tachycardia. Their conclusions were:

"1. In two attacks of paroxysmal tachycardia in which the pulse was upward of 200, the minute-volume sank from 5 to 6.1 liters to

2.8 to 2:1 liters per minute, or roughly, to half to a third of the normal volume.

"2. The degree of ischemia was particularly marked in the skin, as shown by analysis of the blood from the basilar vein.

"3. There was no reduction in the saturation of the arterial blood, but if anything a rise.

"4. The depth of the respiration was reduced to nearly half the normal while the rate was about doubled.

"5. The systolic output 77.5 to 12.9 cc.

"6. The total oxygen consumption of the body was also considerably lowered during two of the attacks."

Carter and Stewart,⁵ in their study of a case of paroxysmal tachycardia, are somewhat at variance with these conclusions. They found a marked decrease of oxygen saturation of the arterial blood. A stagnant anoxemia due to slowing of the circulation brought about by the tachycardia through a greatly decreased output per beat was noted by both groups of observers.

The most noticeable change in the patient here studied, clinically, was a rapid increase in the anasarca with a reduction in urinary output. There did not appear to be any appreciable increase in the degree of respiratory distress. The respiratory rate remained between 20 and 28 per minute.

Cardiac pain was entirely absent during the period of the paroxysm. This is of interest in connection with the consequent lowering of aortic pressure due to the diminution of ventricular output. The highest systolic reading during the attack was 80. The lowest was 65. The systolic and diastolic pressures were incapable of differentiation. Only one single beat marked the auscultatory sounds over the brachial artery. On the second day after the cessation of tachycardia the systolic blood-pressure was 110 and the diastolic was 100.

The prolonged period of the paroxysm offered an excellent opportunity for trying the effect of various remedies and procedures. Vagus pressure did not appear to influence the rate. The only suggestive positive effect was obtained with quinidin sulphate. Quinidin sulphate 0.4 gm. was administered by mouth at 9 P.M., 11 P.M., and 2 A.M. on the night preceding the cessation of the paroxysm. Its influence can be only speculative. Singer and Winterberg⁶ report its successful use in paroxysmal ventricular tachycardia. Owing to the apparent influence on the paroxysm the patient continued the use of 0.4 gm. twice daily. The patient himself felt that his palpitation was greatly decreased by the remedy. It is of interest to note that the only other prolonged attack, which lasted apparently thirteen hours, occurred after the abolition of quinidin for one week.

Conclusions. 1. A case of paroxysmal ventricular tachycardia of unusual duration is presented. Again emphasized is the association

of this disturbance of cardiac mechanism with grave myocardial disease, especially coronary thrombosis.

2. The electrocardiogram shows the dissociated auricular activity with unusual clearness. The tracing also presents an unusual alternation of the ventricular complexes.

3. The therapeutic value of quinidin sulphate in paroxysmal ventricular tachycardia is debatable. It is tenable that good may come of its further study and usage.

BIBLIOGRAPHY.

1. Robinson, G. C., and Herrman, G. R.: Paroxysmal Tachycardia of Ventricular Origin and its Relation to Coronary Occlusion, *Heart*, 1921, 8, 59.
2. Strong, G. F., and Levine, S. A.: The Irregularity of the Ventricular Rate in Paroxysmal Ventricular Tachycardia, *Heart*, 1923, 10, 125.
3. Wölferth, C. C., and McMillan, T. M.: Paroxysmal Ventricular Tachycardia; Report of One Case with Normal Type of Auricular Mechanism and Three with Auricular Fibrillation, *Arch. Int. Med.*, 1923, 31, 184.
4. Barcroft, J., Boch, A. V., and Roughton, F. J.: Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, *Heart*, 1921, 9, 7.
5. Carter, E. P., and Stewart, H. J.: Studies of the Blood Gases in a Case of Paroxysmal Tachycardia, *Arch. Int. Med.*, 1923, 31, 390.
6. Singer, R., and Winterberg, H.: Chinin als Herz- und Gefässmittel, *Wien. Arch. f. inn. Med.*, 1921, 3, 329.

A CASE OF TRYPANOSOMIASIS TREATED WITH TRYPARSAMIDE.

BY HUGH J. MORGAN, M.D.

(From the Hospital of the Rockefeller Institute for Medical Research, New York.)

Introduction. Cases of African sleeping sickness, or trypanosomiasis, are rarely seen in temperate climates and an opportunity for making a careful study of either the manifestations of the disease or its treatment is seldom afforded. Moreover, the present case is of interest because of the fact that the patient was treated with "Bayer 205" and with tryparsamide. Both of these drugs have aroused a great deal of interest on account of the favorable results which have been reported from their use in trypanosomiasis. Exceptionally good results have also been reported from the use of tryparsamide in neurosyphilis. It is for these reasons that the following case report is published.

History Report.—CASE (History No. 4707), female, aged forty-one years, white, missionary. Admitted February 26, 1923; discharged May 24, 1923.

Summary. Onset in the Belgian Congo, October, 1919, with attacks of fever associated with lassitude and asthenia. Crescentic and annular erythematous rash and general glandular enlargement noted in December, 1919, while en route to the United States. The

rash disappeared after eight months, but the glandular enlargement persisted, together with undernutrition and asthenia. Generally "weak and run down" during 1920 and 1921. Bilateral otitis media and antrum infections. In February, 1922, her weight was only 42.2 kg., and there developed increasing asthenia, diplopia, ataxia, general tremulousness, drowsiness and amenorrhea. Disturbance of the senses of taste and smell. Steady failure until July, 1922, when, after the demonstration of *Trypanosoma gambiense* in blood, lymph gland and cerebrospinal fluid, she received 3 doses of atoxyl. Progress of disease apparently arrested. Ten doses of "Bayer 205" with steady improvement, so that in December, 1922, she was symptomless except for slight asthenia and anorexia. Weight 50 kg. In January, 1923, a relapse occurred, with return of former symptoms, together with "lightning" pains in shoulders and symptoms suggestive of mental deterioration. Her weight on admission was 43 kg. Physical examination revealed moderate secondary anemia, extremely dry skin, general glandular enlargement, pyorrhea alveolaris, blood-pressure 80/60, splenomegaly, tremor of tongue, facial muscles and extremities, general muscular weakness, positive Romberg's sign and unsteady gait, poor coördination of movements of extremities, hyperactive deep reflexes, slight muscular rigidity, poorly sustained left ankle and patellar clonus, positive Babinski's sign on the left side, and somnolence. Temperature 99.5° to 102° F. Blood, cerebrospinal fluid and extirpated lymph node negative for trypanosomes. Cerebrospinal fluid contained 30 cells per c.mm. and globulin. Wassermann tests on blood and cerebrospinal fluid negative. Symptoms unabated for a period of three weeks, at end of which time a course of 10 doses of tryparsamide was given, with prompt subjective and objective improvement. Spinal fluid changes slight. Has remained symptomless to date.

Complaint. The patient complained of weakness, unsteadiness and drowsiness.

Family History. Her family history was unimportant.

Past History. Her general health has been good. She had measles, mumps, chicken-pox, and pertussis during childhood. At the age of ten she had typhoid fever from which she recovered without complications. There have been no other diseases and, until onset of the present illness, she has enjoyed unusually good health. Her menstrual periods began at the age of thirteen years; they were at first accompanied by pain but soon became normal.

She married a missionary in 1910 and went with him to the Belgian Congo in 1911. After about six months she returned to the United States where a baby was born in 1912. This child died at the age of seven months from an undetermined cause. In 1912 the patient was rejoined by her husband and they lived in New York until 1914, when a second child was born. The latter is living and well. In 1916 the couple returned to the Belgian Congo.

Present Illness. The first symptom referable to the present illness was noted in 1919. Prior to this time her health had remained good in spite of the conditions under which she lived. Her usual weight was 120 pounds. However, in October, 1919, a very definite change in her health occurred. Within a period of two weeks she experienced three febrile periods, each lasting from three to four days. During these attacks her temperature reached 103° to 104° F. The attacks were separated by afebrile intervals of from one to two days. Because of the fever, she left her station, Tshumbiri, on the Congo River, and returned to Kimpese, from which point, after about two weeks of weakness and lassitude, she went to a port and boarded a steamer for the United States, *via* Plymouth. In December, during her voyage home, the patient thinks that she had no fever. She felt weak, however, and noted that lymph nodes in the neck, axillæ, and groins were enlarged. At this time a curious skin eruption appeared over the back and abdomen; the lesions were erythematous, and were annular or crescentic in shape. The usual lesion was a partial or complete circle of red, mottled skin surrounding a perfectly normal central area. These circles, or crescents, varied from 5 to 8 cm. in diameter, were not elevated, and caused the patient no discomfort.

On her arrival in the United States in January, 1920, the patient did not consider that she was sick, although the skin eruption and glandular enlargement persisted. She was sent to a hospital for the routine examination required by her Missionary Board and was told that, except for slight anemia, she was in good condition. No explanation was offered as to the cause of the skin rash and adenopathy. During the remainder of 1920 the patient lived in Chili, N. Y., and was occupied with the usual duties of a housewife. The rash disappeared after about eight months. She had, during this period, bilateral otitis media and antrum infections which cleared up slowly. She "was not strong" and attributed the feeling of weakness and of lassitude to her previous stay in Africa. The menstrual periods were regular. In February of 1922 there was a change for the worse. Asthenia and anorexia became more marked, and her weight was reduced to 42.2 kg. Amenorrhea developed. She first noted drowsiness and diplopia at this time. Unsteadiness of station and gait developed, together with a coarse tremor of the extremities. The sense of taste and of smell became impaired. Because these symptoms continued to get worse, in July she visited a western clinic where *Trypanosoma gambiense* were found in the blood, in a lymph node, and in the cerebrospinal fluid. She was given 3 doses of atoxyl and advised to go to a London hospital for further treatment. She arrived there in August, 1922, and received 10 intravenous treatments of "Bayer 205."¹ There was marked improvement in all symptoms and she returned to the United States in November, 1922, feeling well. She had gained 3.5 kg. in weight,

the tremor and drowsiness had disappeared and her gait was quite normal. The sense of taste and of smell had returned, and the menstrual periods were reestablished. Her appetite was rather poor. She again took up her household duties.

In January, 1923, she experienced a return of most of her former symptoms, including weakness, unsteadiness, drowsiness, impaired sense of taste and smell, amenorrhea, anorexia and loss in weight. A new symptom developed in the form of severe "lightning" pains in both shoulders and arms. On admission to this hospital on February 26, 1923, she complained of the symptoms enumerated above and also that her memory was poor. She felt that her whole personality had changed. She was depressed and, though her insight was good, she was indifferent as to the outcome of her illness.

Physical Examination. Temperature 99.2° F., pulse 80, respiration 20. Height 156.5 cm. Weight 43.6 kg.

She was a well-developed, poorly-nourished, pale, white woman, who appeared to be about forty-eight or fifty years of age. She was indifferent and apathetic. Insight as to her condition was good and she coöperated fairly well throughout the examination, though it was with difficulty that she remained awake. The skin over the entire body was dry and atrophic. Over the hands and feet the skin was also thick, shiny, darkly pigmented, and somewhat scaly. No gauntlet effect was present. There was no rash. The mucous membranes were pale but otherwise normal.

The cervical, axillary and inguinal lymph nodes were easily palpable, averaging 1.0 to 1.5 cm. in diameter, and were firm and somewhat fixed; they were not tender. Small, firm epitrochlear lymph nodes were palpable.

All the upper teeth and the lower right molar teeth had been extracted. The remaining teeth showed marked pyorrhea.

An examination of the lungs was negative. A soft systolic murmur was heard at the apex of the heart. The peripheral bloodvessels were soft, the pulse small, and the blood-pressure 80/60.

The spleen descended to the costal margin on deep inspiration and was rather soft. The lower poles of both kidneys were palpable.

Neurological Examination. An ophthalmoscopic examination revealed no abnormalities. A marked tremor of the muscles of the face, particularly of those about the eyes, was present. The tongue showed a rather coarse tremor. Otherwise the examination of the cranial nerves was negative.

A marked general weakness was present. No weakness or paralysis was noted in special muscle groups. The patient stood with feet well apart and took short, uncertain, hurried steps. Romberg's sign was slightly positive. Coördinated movements were poorly performed. No disturbances were demonstrated in the sense of touch, pain, or temperature. Deep hyperesthesia was present over the long bones. The deep reflexes were moderately

hyperactive. There was slight muscular rigidity. Babinski's sign was positive on the left side and negative on the right. A poorly sustained clonus of the left ankle and patella was obtained. The abdominal reflexes were present.

Laboratory Examinations. Urine: Specific gravity: 1010-1018. Reaction: acid. Albumin: negative, or only trace. Sugar: negative. Microscopical examination: negative.

Phthalein excretion: first hour 40 per cent; second hour 12 per cent; total 52 per cent.

Blood: Red blood cells, 4,672,000; hemoglobin, 82 per cent (Sahli); white blood cells, 9800.

Differential count (in percentages): Polymorphonuclears, 67.0; basophiles, 0.5; eosinophiles, 6.0; large lymphocytes, 7.0; small lymphocytes, 16.5; large mononuclears and transitionals, 3.0.

Stained film: Erythrocytes showed slight central pallor. The platelets were unusually large. Several examinations of "thick" preparations revealed no parasites.

Wassermann reaction (blood): negative.

Cerebrospinal fluid: Pressure not increased. Cells, 20; globulin, ++. Wassermann reaction (2 cc), negative. Colloidal gold curve, 2224331000. Parasites in centrifugalized sediment, none.

Roentgen-ray of skull, chest and tibiae, negative; basal metabolic rate, normal; stool examination, negative.

One specimen of blood, 2 of cerebrospinal fluid, and an emulsion of an extirpated axillary lymph node were injected into guinea-pigs, rats and mice; these animals remained normal and, while under observation, showed no evidence of trypanosome infection.

Course in Hospital. For a period of twenty-three days the patient was kept in bed on a full diet with extra nourishment. No drugs were administered during this time. On this regime she gained 2 kg. in weight. However, her mental condition showed but little improvement. She remained indifferent and apathetic and had intermittent mild headaches. At times during this period she became a little brighter, but in the main she was dull and drowsy. Her appetite was poor; she had to be fed by a nurse because of weakness. She was careless of her personal appearance. She rarely talked to the nurses or attendants. The pains in her shoulders persisted, but were not so severe. Curious jerking movements of the left thigh were noticed. The tremor and poor coördination persisted, and fever was present. A second lumbar puncture, performed on March 15, showed: 30 cells, globulin + + +, and no parasites.

On March 20, 2 gm. of tryparsamide were given intravenously. As will be seen from Chart I, the temperature immediately fell to normal. A remarkable change in the mental condition was noted during the following week. She became much brighter, more interested in her surroundings and in her personal appearance. She spontaneously engaged in conversation, was less drowsy, and her

appetite improved so that she began to look forward to her meals and to feed herself.

During the period between March 20 and May 21 the patient received 10 doses of tryparsamide intravenously, a total of 23.0 gm. of the drug being given. Improvement was continuous. Her personality changed from that of a depressed, indifferent, careless, lethargic individual, to one of a bright, interested, talkative, optimistic woman. The tremor of the face and extremities slowly disappeared. The headaches and pains in the shoulders and jerky movements of the left thigh were no longer troublesome. The reflexes became normal and Babinski's sign negative. Her station and gait were now normal. She gained, during this period, 10 kg. in weight, and the menstrual periods returned. The blood-pressure rose to 110/75. The spleen remained just palpable. Cerebrospinal

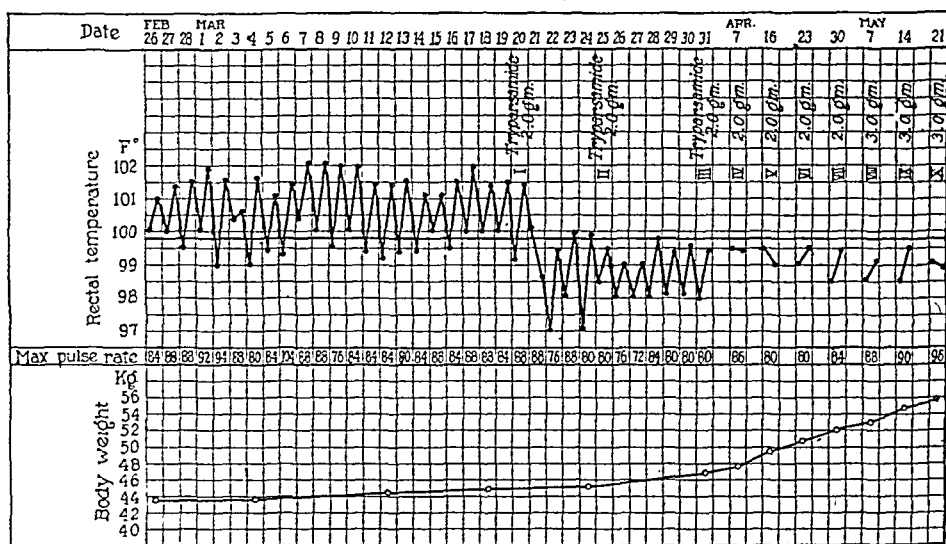


CHART I.

fluid obtained May 3 showed 20 cells and globulin ++. The colloidal gold curve was 2222331000, and the Wassermann reaction negative.

She was discharged, symptomless, May 24, 1923. On July 5, 1923, the patient returned for examination. She had remained entirely symptomless since May except that the last two menstrual periods have been missed. The spleen could still be felt and the deep reflexes were possibly slightly exaggerated. The maximum rectal temperature during the thirty-six hour period of observation was 100.1° F. Except for increase in the hemoglobin (95 per cent) the blood was essentially unchanged. Examination of the cerebrospinal fluid: 12 cells; globulin +; Wassermann reaction negative, colloidal gold curve 2233321000. The urine examination was negative except for a trace of albumin.

Discussion. **DIAGNOSIS.** On admission to this hospital the case was clinically one of recurrent encephalitis. Since trypanosomes had been demonstrated seven months prior to our period of observation, and at a time when the patient was suffering from symptoms almost identical with those which caused her to come to us, it seemed almost certain that the encephalitis was associated with the trypanosome infection.

In the absence of demonstrable trypanosomes, one is forced to assume either (1) that the organisms were present but in localities not accessible when approached by the ordinary routes, or (2) that the patient no longer harbored them. If the latter possibility held, we must assume that the clinical picture was produced by a degenerative process in the central nervous system, the result of a previously active infection. It would seem from the history that this is unlikely. The rather abrupt recurrence of symptoms in February, 1923, with fever and a marked constitutional reaction, is significant. Moreover, these symptoms were identical with those marking a stage in the disease when infection was known to be active in the sense that trypanosomes were demonstrated. That trypanosomes were not demonstrated in the 1923 relapse, either in an excised lymph gland, the blood, or the cerebrospinal fluid, is not remarkable, when one recalls that during the preceding seven months the patient had received 3 doses of atoxyl and 10 doses of "Bayer 205."

TREATMENT. But slight improvement followed the general therapeutic measure employed during the first three weeks the patient was in the hospital. Treatment with tryparsamide was then started.

Tryparsamide is the sodium salt of n-phenylglycineamide-parsonic acid. It was first made in 1919 by Jacobs and Heidelberger.^{2 3} It was shown, by Pearce and Brown,^{4 5} to possess marked therapeutic activity in experimental trypanosome infections and to be relatively speaking, non-toxic.⁶ They concluded that, in the experimental disease, it was superior to many of the drugs commonly employed in the treatment of human trypanosomiasis (atoxyl, arsenophenylglycin, salvarsan, neosalvarsan, etc.) In 1921, Pearce⁷ reported favorably upon the action of the drug in 77 cases of human trypanosomiasis caused by *Trypanosoma gambiense*, and Chesterman⁸ has recently reported favorably upon its effect in 40 cases of the disease.

Doses of 2 and 3 gm. of the drug were employed. They were, in each instance, dissolved in sterile distilled water and given intravenously at approximately weekly intervals. No untoward drug reactions occurred and clinical improvement was immediate. The temperature fell to normal, the headache and somnolence disappeared, and the patient became bright and active mentally. The appetite improved and there was a rapid gain in weight and strength. The tremor became much less marked and Babinski's sign dis-

appeared. When she was finally allowed to walk, her station and gait had become normal, her coördinated movements were well performed, and Romberg's sign was negative. The pains in the shoulders gradually lessened in frequency and intensity, and the deep hyperesthesia disappeared. Her color improved and the menstrual periods were reëstablished. When discharged, May 24, and when seen again July 5, the patient seemed practically normal except for some emotional instability. The spinal fluid at the latter date still showed globulin, a slightly increased cell count, and an abnormal colloidal gold curve. She is to write at monthly intervals, and to report in person for physical examination and lumbar puncture every two months.*

The discussion of the mode of action of the drug used in the present case is necessarily purely theoretical. The absence of demonstrable trypanosomes prior to treatment makes it uncertain that the beneficial action of the drug was due solely to its trypanocidal effect. That organisms may have been present in inaccessible regions of the cerebrum or spinal cord seems likely. The feature of foremost importance in the case is the marked improvement obtained with tryparsamide in a patient showing a clinical relapse after treatment with a trypanocidal agent as powerful as "Bayer 205." If it is assumed that the action of the drug was purely trypanocidal in character, its ability to arrest the course of the disease might be accounted for either by the fact that its chemical nature is entirely different from that of the drug previously used, or by the assumption that tryparsamide was capable of developing a high degree of therapeutic activity in the central nervous system. This assumption is supported by both experimental and clinical evidence. However, the possibility that a general, non-specific action of the drug played a role in the results obtained in this case should be borne in mind. It is interesting to note, in connection with this possibility, that Pearce and Brown⁴ observed such an effect in experimental animals treated with tryparsamide. These workers noted, moreover, that in experimental spirochetal infections,⁹ tryparsamide, while not in itself a powerful spirocheticide, did modify or control the course of the infection. It is possible that this non-specific effect may have been, in part, responsible for the results recently obtained with tryparsamide in the treatment of paresis¹⁰ and one naturally conjectures as to the possible usefulness of the drug in chronic diseases other than those caused by protozoa.

* The patient was readmitted to the hospital October 2, 1923, for a second course of treatment with tryparsamide. At this time she was symptomless and the physical examination was entirely negative. A trace of globulin persisted in the spinal fluid. The cell count was 3 per c.mm. and the colloidal gold curve was negative. She was again admitted to the hospital in March, 1924, and found to be in excellent physical condition.

Prognosis. In the light of the history one is inclined to give a guarded prognosis as to the ultimate outcome of the case. As long as the spinal fluid shows pathological changes, the case cannot be pronounced cured, in spite of the excellent general condition of the patient, and the absence of definite symptoms of neurological disease.

Summary. A report is made of a case of African trypanosomiasis in which a relapse occurred after treatment with atoxyl and "Bayer 205." The results of treatment with tryparsamide are given, together with a brief theoretical discussion of the mode of action of the drug.

BIBLIOGRAPHY.

1. Low, G. C., and Manson-Bahr, P.: *Lancet*, 1922, **207**, 1265.
2. Jacobs, W. A., and Heidelberger, M. J.: *Jour. Am. Chem. Soc.*, 1919, **41**, 1587.
3. Jacobs, W. A., and Heidelberger, M. J.: *Jour. Exp. Med.*, 1919, **30**, 411.
4. Pearce, L., and Brown, W. H.: *Jour. Exp. Med.*, 1919, **30**, 437.
5. Pearce, L., and Brown, W. H.: *Jour. Exp. Med.*, 1919, **30**, 455.
6. Brown, W. H., and Pearce, L.: *Jour. Exp. Med.*, 1919, **30**, 417.
7. Pearce, L.: *Jour. Exp. Med.*, 1921, **34**, No. 6. Supplement No. 1.
8. Chesterman, C. C.: *Tr. Roy. Soc. Trop. Med. Hyg.*, 1923, **16**, 394.
9. Pearce, L., and Brown, W. H.: *Jour. Exp. Med.*, 1919, **30**, 483.
10. Lorenz, W. F., Loevenhart, T. A. S., Bleckwenn, W. J., and Hodges, J. A.: *Jour. Am. Med. Assn.*, 1923, **80**, 1497.

SYPHILIS AS THE CAUSE OF MUSCULAR ATROPHY OF SPINAL ORIGIN.*

BY ALFRED J. OSTHEIMER, M.D., L.R.C.P. (Lond.), M.R.C.S.
(Eng.), GEORGE WILSON, M.D.,

AND

N. W. WINKELMAN, M.D.

PHILADELPHIA.

(From the Neuropsychiatric Section of the U. S. Veterans' Bureau, District No. 3, Philadelphia, Pa., from the Neurological Department of the School of Medicine of the University of Pennsylvania, and from the Neuropathologic Laboratory of the Philadelphia General Hospital.)

In his lecture on The Syphilitic Muscular Atrophies (which is one of twenty (20) given during 1921 by noted neurologists of the Paris Faculty of Medicine) André Léri¹ makes the statement that progressive amyotrophies are most commonly, if not always, syphilitic in origin. In 1897 Pierre Marie² questioned whether there

* Publication authorized by the Medical Adviser, U. S. Veterans' Bureau. The cases on which this paper is based were studied at the U. S. Veterans' Bureau, District No. 3, Philadelphia, Pa., the Episcopal Hospital, Philadelphia, Pa., the Philadelphia General Hospital and the University Hospital of Philadelphia.

¹ Questions neurologiques d'actualité, Paris, p. 259.

² Revue neurologique, 1897. Quoted by Léri.

was such an entity as a primary chronic anterior poliomyelitis. In 1903 Léri³ reported 6 cases of spinal progressive muscular atrophy, all of them syphilitic in origin. Two autopsies showed the diffuse vascular lesions of meningomyelitis similar to those observed and described by Raymond in 1893.

In his remarkable paper entitled *Progressive Muscular Atrophy, a Study of the Causes and Classification, with the Report of an Autopsy*, read at the meeting of the American Neurological Association in June, 1905, Dana⁴ went so far as to say, "I have seen so many cases of progressive muscular atrophy that were so distinctly parasyphilitic, that it seems to me that we might infer that nearly all the atrophies were due to this process." And further on he says, "It will be remembered that the investigation into the syphilitic origin of tabes began with rather modest statistics in its support." We were so much impressed with the following portion of Léri's lecture, that we wondered whether the teaching and the general knowledge of this subject were so much more advanced in France than in this country as to warrant the following statement: "This idea (meaning the idea that spinal progressive atrophy is practically always due to syphilis) is now so banal that cases of syphilitic amyotrophy are no longer reported; it can today be stated with assurance that progressive spinal amyotrophy is as much a syphilitic disease as is tabes. There are many cases of actual tabes in which efforts to prove them of luetic origin have failed, both from the standpoint of inheritance and from that of objective examination of the patient, as well as from that of laboratory studies; this is, however, no reason to deny that tabes is syphilitic in origin. Just about as much is true of progressive spinal amyotrophy."

The writers of this paper can hardly believe that in this country the above idea is so "banal" and generally accepted, that these cases are no longer reported, or that the general practitioners and perhaps even the neurologists, have been so impressed with this fact that in the presence of any amyotrophy of unknown cause antisiphilitic treatment is immediately instituted in every instance. It is of interest at this point briefly to record the opinion of different neurologists as expressed in the American standard text books on neurology.

Spiller⁵ in his article on progressive spinal muscular atrophy in *Modern Medicine* says "Some of the cases supposed to represent progressive spinal muscular atrophy are caused by myelitis, especially the syphilitic form. The inflammation may be almost confined to the gray matter and such being the case, sensory disturbance may be absent. The symptoms then would be those of

³ Report of the 1903 Congress of Neurologists and Alienists, published in Brussels.

⁴ *Jour. Nerv. and Ment. Dis.*, 1906, **33**, 81.

⁵ Osler and McCrae, Philadelphia, Lea & Febiger, 1913-15, p. 82.

progressive spinal muscular atrophy, although the lesion would be a diffuse process of inflammatory character."

This same writer,⁶ in 1912, wrote a paper on syphilis as a possible cause of systemic degeneration of the motor tract. In this article he reported several cases of muscular atrophy occurring in spinal syphilis. Spiller there said: "There is no objection on a *priori* grounds in accepting syphilis as a possible cause of various diseases of the motor system, as primary lateral sclerosis, amyotrophic lateral sclerosis, and progressive spinal muscular atrophy."

In Church and Peterson's⁷ text-book, much used by medical students and practitioners, under the heading Etiology in the article on progressive muscular atrophies, presenting lesions of the spinal gray matter, occurs this sentence, "Since the Wassermann and spinal fluid tests have been available, positive findings in these cases indicate that syphilis is a more common feature, if not an actual cause, than was formerly supposed."

Dana, under the heading of Progressive Muscular Atrophy in the ninth edition of his text-book says "All three types of atrophy may be caused by syphilis, and hence the disease may occur in locomotor ataxia. Usually, however, syphilis causes an atrophy running a rather special course." In a footnote he states: "Among 72 cases, four-fifths were in males, syphilis was present in about one-fifth of the cases," and "on the whole the dominant causes are an occupation strain, syphilis, and some inherited weakness of the affected neurones."

White and Jelliffe⁸ under the heading Progressive Muscular Atrophy, says "Here heredity may play a part in the development of a familial form, seen in infancy and also in adults (Bernhardt). It may follow acute poliomyelitis. Other factors, as toxemias, trauma, cold, wet, overexertion, are not definitely established. Occupation atrophies are at times incorrectly included here."

Case Reports. The subject is one of great practical importance and we desire to report the following cases as instances of spinal muscular atrophy due to syphilis:

CASE I.—A white male, aged thirty-three years, a motorman, was examined at the U. S. Veterans' Bureau, District No. 3, on December 20, 1922. He does not use alcohol; he has been married four years and has three children, all of whom are living and well. He had a chancre fourteen years ago. His military history is of no importance except that he suffered from so-called "rheumatism" while in the army.

⁶ Syphilis a Possible Cause of Systemic Degeneration of the Motor Tract., Jour. Nerv. and Mental Dis., 1912, 39.

⁷ Nervous and Mental Diseases, Philadelphia, W. B. Saunders Company, 1921, p. 408.

⁸ Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1917, p. 413.

Present Illness. This man has complained of pain ever since he has been in the service. The pain he describes as dull, stiff and achy, and at times has been sharp and stabbing, especially in the lower extremities. He also has had relaxation of the urinary sphincter. His libido has been much decreased. He has continued his work as a motorman up to the present time.

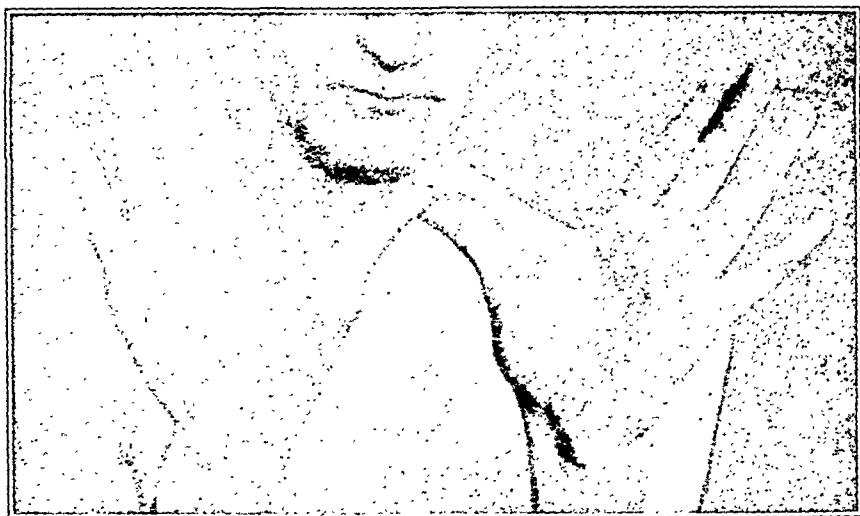


FIG. 1.—Showing atrophy of hands, especially the right.

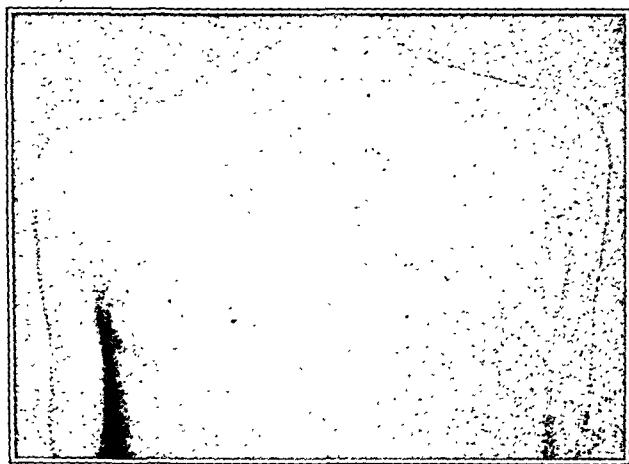


FIG. 2.—Showing atrophy of shoulder muscles.

Physical Examination. The station shows a slight sway but not a true Romberg. The gait is spastic, especially on the right. The deep reflexes in the lower extremities are greatly increased with an abortive ankle clonus on both sides and a typical bilateral Babinski. The deep reflexes of the upper extremities are present, but are greatly diminished. The man's muscular development is very poor, there being a generalized wasting; the small muscles of the hand and the muscles of the shoulder girdle (Figs. 1 and 2)

show real atrophy especially on the right, and marked weakness is present in all four extremities.

Electrical reactions show a marked diminution in the contractibility in response to the faradic current in the atrophied muscles. Fibrillary contractions are present in the muscles of the arms and shoulder girdles. The tongue and lips are not involved. The pupils are equal, slightly irregular and react well to light and in accommodation. All forms of sensation are normal throughout the body. The patient is bright mentally and shows no evidence of cerebral involvement.

On January 5, 1923, the blood Wassermann was strongly positive and the spinal fluid Wassermann was negative. The albumin and globulin were increased in the spinal fluid which showed three cells per c.mm. The colloidal-gold test showed no curve. The roentgenogram of the cervical and upper dorsal spine was negative.

This case, with the exception of the pain and sphincter disturbance, would have passed for a case of amyotrophic lateral sclerosis, the picture of which the man presented. The symptoms came on nine years after the initial lesion, that is, five years ago. From certain facts in the history it is clear that the whole condition is one of syphilis of the spinal cord. Since antisyphilitic treatment has been instituted the patient has greatly improved.

CASE II.—A white male, at present aged thirty-nine years, a machinist, was admitted to the Episcopal Hospital on August 14, 1916. His family history was negative. Before his admission to the hospital he used alcohol and tobacco moderately. He had a chancre at the age of eighteen years, in 1902. He was married in 1904 and his wife, who died in 1907, had two miscarriages. This man's trouble began in 1906, the first thing he noticed being weakness of the right hand followed in a short time by wasting of this part and by a wrist drop. The condition then spread to the left hand and wrist, then to the remaining portions of both upper extremities and shoulders, then to the lower extremities and trunk. From the onset until the whole body was involved was eight years. His weight dropped from 172 pounds to 90 pounds.

Physical Examination (February 24, 1923). The pupils are irregular and react poorly to light, but well in accommodations. No cranial nerve palsies are present. The tongue is larger than normal, presenting many deep fissures and resembling the so-called scrotal tongue. The man presents intense atrophy of all muscles from the neck down (Figs. 3 and 4); some of the muscles, especially those of the buttocks are the seat of fibrillary tremors. All of the deep reflexes are lost. Plantar stimulation produces flexion on both sides. No voluntary movements are present in the left upper extremity; in the right upper extremity a little flexion is possible at the elbow with a fair amount of pronation and supination.



FIG. 3.—Generalized atrophy with deformity.

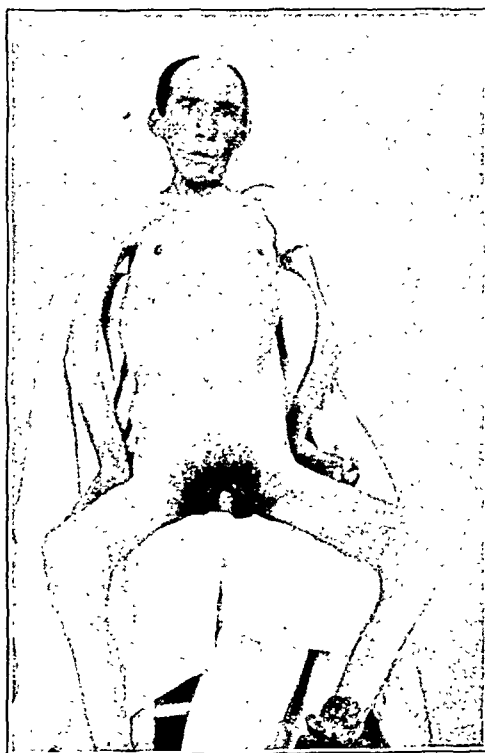


FIG. 4.—Generalized atrophy with deformity.

The man can turn over in bed, but in so doing he goes through a number of contortions. More power is preserved in the lower extremities than in the upper, movements at the ankles, knees and hips being possible but very weak. The man has a wasp waist. Sensation is normal.

The result of the examination of the eyes by Dr. Fewell on February 28, 1923 is as follows: The discs are dusky and the margins well developed. The smaller vessels are quite tortuous and the veins pressed upon. No lesions of the choroid or retina were seen. The diagnosis is angiosclerosis.

The Wassermann examination of the blood made at the Philadelphia General Hospital, June 12, 1913 was three plus. The blood Wassermann examination at the Episcopal Hospital on March 1, 1923 was negative. The patient has never submitted to a lumbar puncture.

The atrophy in this case began four years after the patient contracted a chancre. His age at the onset was twenty-two, a late age for dystrophy and an early one for progressive spinal muscular atrophy. The condition of his pupils and of his tongue are strongly indicative of syphilis. At one time he had a strongly positive Wassermann although the reaction at present is negative.

CASE III.—A Chinaman, aged forty-eight years, was admitted to the Philadelphia General Hospital on December 11, 1920. He was assigned to the service of Dr. Charles S. Potts, through whose courtesy we are reporting this case. The man had a chancre in 1904.

Present Illness. In March, 1920, the patient noticed that he had difficulty in swallowing. Dysphagia progressed so that by the time he was admitted to the hospital he could swallow nothing but liquids. He has lost a great deal of weight.

Physical Examination. Atrophy of the muscles of the upper extremities was present and marked with a great diminution of power in these parts. The lower extremities showed slight atrophy and weakness, but all movements were possible. The biceps, triceps and patellar reflexes were present and increased and a bilateral Babinski was present. Ankle clonus was not obtained. His station and gait, and the finger-to-nose test could not be determined because of weakness. Sensation was normal throughout. The pupils were unequal and irregular and reacted sluggishly to light; weakness of both sides of the face was present. The tongue presented a tremor, was atrophic and could not be protruded. The lips were widely separated; the man could not whistle, and could not blow out a lighted match, and could not talk. He could not swallow solids, and weakness of the soft palate was present. An examination of the spinal fluid was never made, but the blood Wassermann was positive. This patient died on March 19, 1921, and no autopsy was obtained.

This case is one which clinically resembles amyotrophic lateral sclerosis beginning as a bulbar palsy. A clear history of syphilis sixteen years before the onset of the amyotrophia was obtained, and the blood Wassermann was positive. The state of his pupils also pointed to syphilis as the etiological factor in the disease of the nervous system.

CASE IV.—A white male, unmarried, aged fifty-two years, a brass worker for thirty-five years, was admitted to the Philadelphia General Hospital and was assigned to Dr. Charles W. Burr's service October 9, 1921. He died about five months later, on March 19, 1922, while under the care of Dr. D. J. McCarthy, through whose courtesy the report of this case is made possible.

History. The family history was negative; the patient had malaria at thirteen years of age and has had chills and fever at irregular intervals ever since. On admission he complained of loss of power in both arms, pains throughout the arms and legs; headache, loss of power of the lower extremities and loss of bladder and bowel control. A regular rise of temperature in the afternoon was noted. The onset of the condition was in 1913, marked by numbness and tingling in the left hand and with loss of power in the fingers, which gradually involved the muscle groups of the elbow and shoulder. In 1915 the right upper extremity became involved and the atrophy on this side developed rather rapidly. A fracture of the left hip, due to a fall, occurred in 1918 and as a result the left leg has been about four inches shorter than the right. Just before admission, weakness in the legs developed with sharp, shooting pains on both sides. There has been a loss of 20 pounds within twelve months prior to admission.

Physical Examination. The man was found to be much emaciated and had the general appearance of one of seventy rather than of fifty-two. Diplopia was present; the left pupil was slightly larger than the right, and both reacted sluggishly to light but well in accommodation. The left biceps and triceps reflexes were present on the left but on the right side were absent. Both patellar reflexes were absent and there was no clonus. Plantar stimulation resulted in flexion. All the muscles of both arms were markedly atrophied, including the muscles of the shoulder girdle. There was marked diminution in the power of the left upper extremity and the left hand was a typical "main en griffe." There was no motion possible in the right arm except at the wrist and slight flexion of the elbow. Fibrillary tremors were present throughout the muscles of the arm. While there was some atrophy in both legs, it was only slight. Sensation was normal and loss of sphincter control of bladder and rectum was evident. Marked arteriosclerosis with blood-pressure of 180/90 was noted. Kyphosis and scoliosis were present. The cranial nerves were normal. The Wassermann test

of the spinal fluid was four plus. The urine showed some albumin and casts.

Pathology. Microscopically the cord is so small and distorted that it is difficult to distinguish the various levels. The anterior horns are smaller than usual and contain fewer nerve cells throughout (Fig. 5). The least involvement is in the lower lumbar and sacral regions but even here the cells show degeneration. The type of cell change varies—simple atrophy predominates, although lipoid degeneration is present. The glia elements are increased. The anterior roots are degenerated to a large extent (Fig. 6).



FIG. 5.—Anterior horn cells, lower cervical region showing marked decrease in number and many small atrophic cells present with increase in glia nuclei. Kresyl violet, $\times 80.5$.

Clarke's columns are well preserved and stand out in marked contrast to the few and atrophic anterior horn cells. The posterior columns show sclerosis more marked in the upper cord (Figs. 6 and 7). Lissauer's tract is likewise degenerated as are also the posterior root fibers. The lateral columns are uninvolved. The meninges are thickened and contain a few small round cells mainly of the lymphocytic type (Fig. 8) especially noticed around the vessels. A fibrous hyperplasia is also present. The vessels throughout the cord show definite sclerosis (Fig. 9).

The medulla shows no changes aside from slight meningeal infil-



FIG. 6.—Thoracic cord, showing almost complete posterior column degeneration with some distortion of the cord. (Weigert.)



FIG. 7.—Thoracic cord, showing same as Fig. 6, with distortion of anterior horns.

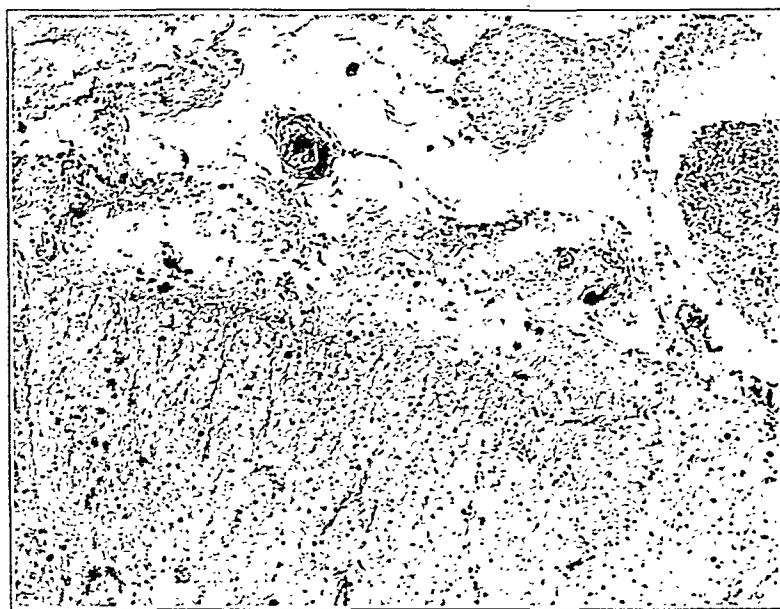


FIG. 8 —Pia-arachnoid, showing round-cell infiltration. $\times 115$. Toluidin blue stain.

tration and sclerosis of its vessels. Unfortunately the peripheral nerves and muscles were not removed nor were the intestines very carefully examined.

Pathological Diagnosis. Meningomyelitis (syphilitic type).



FIG. 9.—Anterior spinal artery cervical cord, showing endarteritis with splitting of elastic lamina (a). $\times 115$. H. and E. stain.

CASE V.—A white widow, aged fifty-five years, came to the neurological dispensary of the hospital of the University of Pennsylvania on March 6, 1923. Her chief complaint was weakness of the left arm and hand.

The patient was married for ten years when her husband died. She had one stillborn child. No other pregnancies. She denies the use of alcohol.

We are able to report this case through the kindness of Dr. William G. Spiller.

Present Illness. About nine months ago the woman noticed weakness of her left hand; she first observed this because she frequently dropped articles from her hand. The weakness gradually progressed, until at the end of two months she was unable to use her hand to any extent. About this time she noticed that the hand was becoming smaller. She has had not pain although at times she has a jumping sensation in her arm. She has no trouble with her eyesight, and no sphincter disturbance. Her right hand has not been affected although she says it has a queer feeling.

Physical Examination. The pupils are equal, regular and react well to light and in accommodation. Examination of the eye-grounds shows that the media is clear, the discs round, and of fair color and

good outline. The vessels show moderate sclerosis and there is no fundus lesions.

The left hand is markedly atrophic and is in the claw position. The muscles of the forearm, arm, and especially of the shoulder girdle, are somewhat atrophic. The muscle power of the left upper extremity is much less than that of its fellow, which is about normal. The biceps, triceps, von Bechterew's and patellar reflexes are bilaterally increased. Ankle clonus is not obtained, but plantar stimulation produces extension of the great toe on both sides. Sensation is normal throughout. The tongue and lips show no atrophy. The electrical reactions in the small muscles of the hand show a moderate diminution in contractility in response to the faradic current.

The blood Wassermann was strongly positive. Examination of the cerebrospinal fluid showed a negative Wassermann and colloidal-gold curve, with two cells to the cubic millimeter. The roentgenogram of the cervical and upper dorsal spine was negative.

This case of nine months' duration shows intense atrophy of the left hand and moderate atrophy of the remaining portion of the left upper extremity with a marked increase of all the deep reflexes, and a bilateral Babinski, a picture which is comparable in every way to an early stage of amyotrophic lateral sclerosis. With a strongly positive reaction of the blood we believe we are justified in considering this case one of spinal syphilis involving the anterior horns and the lateral tracts.

Since the time when, in 1893, Raymond definitely established a relationship between syphilis and progressive muscular atrophy, by a description of a diffuse meningomyelitis, vascular in origin—and since 1905, when Dana suggested the probability of all spinal muscular atrophies being due to syphilis, and being a clinical form of spinal syphilis, with predilection for the anterior horns, just as Erb's spastic paraplegia is due principally to lesions of the lateral tracts and tabes dorsalis consequent principally upon an involvement of the posterior roots, until today when Léri says "I believe that progressive spinal amyotrophie is always or almost always due to syphilis," how much has our teaching progressed in the way of stressing the importance of treating all such muscular atrophies as parasymphilitic conditions as we have learned to treat tabes dorsalis, thanks to the writings of Fournier in 1876 and of Erb in 1879?

Summary. The amyotrophic form of spinal syphilis is a syndrome actually due to syphilis of the anterior horns and may or may not be associated with a tabes dorsalis or paresis. The object of this paper is an endeavor to focus attention on this point, in the hope that, by the frequent reporting of many cases of spinal progressive muscular atrophy, when syphilis is found to be the cause, and in which postmortem findings demonstrate the syphilitic structural

changes, this knowledge will become so generalized that antiluetic treatment will be immediately instituted, just as it is today in *tabes dorsalis* and paresis.

Of course, any conclusions based on the findings in our own few cases would not be justified. The writers hope to collect data on a sufficient number of cases to warrant some definite conclusions, but take the present moment as an opportunity to awaken the interest of the profession in order that all available cases of this sort may be investigated and reported with postmortem findings, if possible, so that from the mass of data the truth may ultimately be known.

A STUDY OF THE BACTERIOLOGICAL FINDINGS IN THE LYON-MELTZER TEST.

BY W. W. BOARDMAN, M.D.,

SAN FRANCISCO, CALIF.

(From the Gastro-intestinal Clinic, Stanford University Medical School.)

A PROPER understanding of the various factors influencing the bacteriology of the duodenal content has become essential with the introduction of the Lyon-Meltzer method in the study and treatment of the diseases of the biliary system.

For diagnostic purposes, the method briefly consists of the microscopical and bacteriological study of three samples of duodenal material obtained after the installation of magnesium sulphate in 25 to 30 per cent solution. These samples are supposed to be derived from the common duct, the gall-bladder and the hepatic ducts respectively. Admitting such origin, the question naturally arises as to the significance of the bacteriological findings in these samples, especially as to whether microorganisms so found, may be considered of pathological significance, or merely as unavoidable contaminations.

Recalling for the moment that into the duodenum is emptied the gastric chyme, the bile and pancreatic secretions, as well as the secretion of the duodenal mucosa, and at times, material from the small bowel, it would seem evident, that organisms obtained from the duodenal content might have their origin in either the mouth, stomach, biliary system, pancreas or small bowel.

Our present knowledge of the bacteriology of the upper alimentary tract is far from complete. It is well known that innumerable organisms of various types, having their origin in the nose, mouth, throat, lungs and food are constantly being swallowed. It is also rather generally accepted that the acid gastric juice effectually

destroys such swallowed organisms and that the duodenal content is normally sterile.

The work of Cushing and Livingood¹ partially confirms this opinion, as they concluded after careful surgical studies, that in the normal healthy adult, the stomach, duodenum and upper small bowel rapidly become amicrobic in the fasting state. However, they also state that during digestion, numerous organisms having their origin in the ingesta, successfully resist the action of the acid gastric juice, and may be recovered from the duodenum. In their studies, yeast and coccal forms appeared most frequently in the duodenal samples.

Other investigators have attempted studies of the duodenal content by means of the duodenal tube, but their results are less convincing. Thus Hess,² obtaining the samples by means of a small catheter passed into the duodenum of fifteen infants, found *Bacillus coli* once, but staphylococci frequently. Later, MacNeal and Chase³ studied twenty-four adults, using a duodenal tube, the tip of which was protected by a salol coated gelatin capsule to prevent contamination during the passage of the tube. From this series, they concluded that normal duodenal fluid is practically free from living bacteria when food is absent, but that the number of cultivable microbes in the duodenal fluid is markedly increased in variously gastro-intestinal disturbances.

The question naturally arises as to whether samples obtained by the duodenal tube method can be properly compared with those obtained by direct surgical means, in other words, is the duodenum into which a duodenal tube has found its way, a normal fasting duodenum? There can be no question but that the passage of the tube stimulates a more profuse salivary secretion than is present in the normal fasting state, and that a large part of this secretion is swallowed with the tube and while the tube is in the duodenum.

Just what effect the tube has on gastric secretion and peristalsis, may be open to question, but again, there is no doubt that periodically, gastric content is discharged into the duodenum while the duodenal tube is in place. It would therefore seem possible that the findings of Hess² and MacNeal and Chase³ may have been influenced by salivary contamination, which was a less marked factor in the work of Cushing and Livingood.¹

Ample proof is at hand of the very high bacterial content of saliva. Streptococci and staphylococci have been demonstrated in over 80 per cent of fifty-four samples from dyspeptic patients by Smithies. The work of Kopeloff⁴ is of interest in this connection, as he studied the gastric flora during a fractional test-meal. He isolated thirty-two types of organisms from the gastric contents and almost invariably found the same organisms in the saliva and the material of the test-meal, the saliva furnishing the members of the streptococci and staphylococci groups, the test-meal, the remaining groups. He concludes that the bacterial flora of the stomach is almost entirely

dependent upon the saliva swallowed, and also that the degree of acidity plays no appreciable role in determining the type of organism found.

Granting then, the presence of organisms in the stomach, practically all investigators agree that, even with normal acidity, there is abundant opportunity for them to pass unharmed into the duodenum.

With this evidence, we may conclude that although the normal fasting duodenum may rapidly become amicrobic when examined directly, there is no satisfactory evidence that the duodenum of the gastro-intestinal patient is amicrobic when examined in the fasting state by means of the duodenal tube, whereas, on the contrary, there is evidence that the saliva carries an abundant bacterial flora to the stomach and that the gastric flora, to a very large extent, determines the duodenal flora.

The possibility of such contamination of the biliary samples has been more or less clearly recognized by Lyon and some of his followers and two methods have been proposed to prevent it.

Whipple,⁵ following the technic of MacNeal and Chase, used a tube, the tip of which was sealed with a salol coated gelatin capsule, which was not dissolved until the tip had reached the duodenum. By this means, it was thought that contamination with "organisms carried down in the effort to swallow the tube," was at least to some extent prevented. With this technic, he studied 150 cases and boldly concludes that "The colon bacillus, the hemolytic streptococcus and *Staphylococcus aureus*, especially if found in the bile following the magnesium sulphate, may be considered as etiological factors and as probably present in the gall-bladder or common duct or both." Recalling that he has not excluded salivary contamination, as the organisms carried down in the effort to swallow the tube may have gone on into the duodenum and contaminated his bile samples, these seem unjustifiable conclusions.

Lyon,⁶ on the other hand, has attempted to sterilize the mouth and stomach by the use of permanganate and zinc chloride. The following quotation is of interest:

"To make possible accurate diagnosis of the duodenal biliary zone, it is necessary that we adopt means to prevent cytological and bacterial contamination from the mouth, teeth, tonsils, respiratory tract and stomach, from confusing us in our interpretations of duodenal and biliary materials.

"To avoid this as far as possible, I have adopted the following routine method in diagnosis: The patient presents himself with twelve-hour-fasting stomach, he then brushes his teeth carefully, rinses and gargles his mouth and throat thoroughly first with a strong solution of potassium permanganate gr. 1 to 1 ounce, then with a mild astringent solution of zinc chloride. Tube was freshly sterilized by boiling. The fasting content aspirated, is set aside

for chemical, cytological and bacteriological examination for comparison with the findings later recovered from the duodenum. The stomach is then rinsed to sparkling clearness, using gravity douching from 250 cc irrigating tanks or syringe douching and recovering the wash-water in 250 cc conical graduates in which can be noted how clean the stomach is—mucus, shreds, mucopurulent plugs and other material which yields much valuable information. After the wash-return is sparkling clear, the stomach is made astringent with Lavoris and then rewashed thoroughly. It is surprising to observe how often a stomach apparently washed clean, after being made astringent, will press out from the mucosal tubules mucopurulent masses, etc., often swarming with bacteria. After washing again, the stomach is disinfected with 250 cc of 1 to 10,000 permanganate solution immediately recovered, and stomach is again washed clear. This so far as possible, prevents contaminated material from the upper zones, confusing our interpretation of material later obtained from the duodenal biliary zone."

How far do such methods prevent contamination and make possible accurate diagnosis of the duodenal biliary zone? I believe the first method may be dismissed as unsatisfactory, as it is based on the assumption that the organisms found in the duodenum have their origin there, and neglects the contamination of duodenal content occurring with each discharge of gastric content.

The Lyon technic should be of value if it will do that for which it is designed, namely, the sterilization of the mouth, or better, the saliva, for a period of one to three hours, and secondly, the sterilization of the stomach, for an equal period.

As regards sterilization of the saliva, one can readily demonstrate that this is impossible by the method proposed by Lyon. Numerous tests were made on healthy members of the staff—taking cultures of the saliva before applying the Lyon method of treating the mouth, and at half-hour intervals after such treatment, over a period of two hours. In every case, the tubes, after attempted sterilization, were practically indistinguishable from those before, all showing most profuse growths. As it was thus evident that infected saliva was entering the stomach during the course of the routine test, no effort was made to determine the effect of the Lyon method of attempted sterilization of the stomach. In this connection, one statement of Lyon however, is of interest: "It is surprising to observe how often a stomach, apparently washed clean, after being made astringent, will press out from the mucosal tubules, mucopurulent masses, etc., often swarming with bacteria." If such plugs are pressed out by the astringent action of Lavoris solution, it seems probable that other similar plugs are pressed out by peristalsis during the fifteen minutes to two hours consumed by the test.

It seemed perfectly evident that the infected saliva swallowed

during the course of the routine test, eventually finds its way into the duodenum, but to demonstrate that such was the case, we have repeatedly placed a few grains of powdered charcoal on the tongue of patients undergoing the examination, and almost without exception, particles of charcoal have been recognized either macroscopically or microscopically in the bile samples before and after the administration of the magnesium sulphate.

From the foregoing, it is apparent that even with the Lyon technic, infected saliva is being swallowed during the course of the examination, that the organisms thus swallowed are not destroyed by the gastric juice, but are passed on into the duodenum where they may contaminate the various bile samples and render reliable bacteriological conclusions impossible. To investigate this assumption, a series of cases was examined, cultures being made from the pharynx, the fasting gastric content, the fasting duodenal content and the so-called *A*, *B* and *C* bile samples.

Our routine, because of the demonstrated impossibility of sterilizing the mouth, was less elaborate than that proposed by Lyon. Patients presented themselves at eight o'clock in the fasting state and a swab was taken from the tonsil areas, the mouth was then thoroughly rinsed with a 1 to 5000 permanganate solution. A freshly sterilized duodenal tube was then swallowed and the gastric content extracted and a culture made. The stomach was then thoroughly rinsed with a 1 to 10,000 permanganate solution until the washings returned clear. When the tube was apparently in the duodenum, its position was confirmed by fluoroscopical examination, after which, a culture of the duodenal content was made. Sterile magnesium sulphate was then administered and the various samples of bile collected and cultured.

TABLE I.

Source of material.	Cultures, positive.	Cultures, negative.	Specimen not obtained.	Cultures similar to those of:								Cultures unlike.			
				Pharynx.		Stomach.		Duodenum.		"B" bile.		Pharynx and stomach.		Pharynx stomach, duodenum.	
				No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Pharynx	56														
Fasting gastric content	30	16	10	16	53										
Fasting duodenal content	29	17	10	20	69	13	45	5	17		
"B" bile	35	15	6	20	57	16	45	19	54	5	14	2	5
"C" bile	26	18	12	12	46	11	42	12	48	24	92	7	26	2	8

We had for comparison, 56 cases so studied. By referring to Table I, it will be seen that the fasting content, duodenal content,

B bile and *C* bile gave growths similar to that obtained from the mouth in from 46 per cent to 69 per cent of the cases and that the various bile samples gave cultures resembling those of either mouth or stomach in from 74 per cent to 86 per cent of the cases. In other words, in only 14 to 26 per cent of the bile cultures, was there an absence of organisms similar to those found in the mouth and stomach. It is probable that there would have been a closer agreement between the mouth cultures and those of the fasting gastric content, if cultures had been taken from the saliva, rather than by swabbing the tonsil areas. The various types of staphylococci and streptococci were the organisms most frequently found.

Conclusions. With these findings, it seemed apparent to us that no reliance could be placed on the bacteriological findings in the various bile samples and that even with the most painstaking technic, including the study of the mouth and gastric flora, the procedure is bacteriologically so fundamentally faulty that its use in the routine clinical study of the "duodenal biliary zone" is apt to lead to more incorrect than correct conclusions.

BIBLIOGRAPHY.

1. Cushing and Livingood: Contributions to the Science of Medicine, 1900, p. 543.
2. Hess: Jour. Infect. Dis., 1912, 2, 71.
3. MacNeal and Chase: Arch. Int. Med., 1913, 12, 178.
4. Kopeloff: Jour. Infect. Dis., 1922, 30, 613.
5. Whipple: Ann. Surg., 1921, 73, 556.
6. Lyon: New York Med. Jour., 1920, 112, 45.

THE VALUE OF PHYSICAL SIGNS IN THE EARLY DETECTION OF PULMONARY METASTASES.

BY LLOYD F. CRAVER, M.D.,

NEW YORK.

(From the Memorial Hospital, New York.)

The Need for the Early Recognition of Metastases of Malignant New Growths. The early recognition of metastases to the lungs or pleura in those types of malignant tumors in which such metastases are prone to occur is of fundamental importance. For the purposes of this paper it was considered advisable to select two typical examples of such cases; namely, mammary carcinoma and osteogenic sarcoma. Careful physical examination of the chest should form a part of the general survey which a patient suffering from either of these diseases undergoes when first seen. The recognition of metastases at this time has an important bearing both on prognosis and

on the kind of treatment to be carried out. There is no doubt that many breasts have been needlessly amputated and many limbs sacrificed in cases complicated by unrecognized metastases to the lungs or elsewhere at the time of operation. By the early discovery of such metastases not only could these patients be spared an unnecessary operation, but in certain selected cases better palliation could be obtained by the use of radiation, and at the same time additional material would thus be made available for the study of the effect of various kinds of radiation on the various types of these two diseases. There is believed to be some evidence that the operative removal of a primary malignant growth imparts increased growth stimulus to metastases, so that the operation, in such cases, not only does no permanent good, but may actually shorten the life of the patient; while with proper selection of patients, it is possible that a certain number of cases of mammary carcinoma or osteogenic sarcoma with early secondary tumors in the lungs might be benefited temporarily by radiation. To be sure, it seems advisable, at times, to amputate a foul, ulcerating, painful breast or a large painful osteogenic sarcoma, even in the presence of metastases, without any hope of curing, but as the best means of speedy palliation.

Comparison with Pulmonary Tuberculosis. In the examination of cases of pulmonary tuberculosis, it is now generally accepted that reliance cannot be placed entirely on the radiographic plate or film for the detection of incipient cases. In a certain proportion, small, to be sure, but nevertheless well established, the physical signs in conjunction with the anamnesis and other findings, prove the presence of tuberculosis in cases in which the roentgenologist is unable to confirm the diagnosis. On the other hand the clinician is sometimes greatly surprised to find evidence on the roentgen-ray plate of well-marked tuberculosis which he had not suspected, or which he may have suspected from other data, but of which he had been unable to elicit any physical signs. The same situation exists, I think, in pulmonary metastases, especially in mammary carcinoma. Just as in pulmonary tuberculosis, there is, on the whole, close correspondence between the radiographic or fluoroscopical signs and the physical signs; but there are some cases in which the clinician is considerably surprised at the extent of metastatic involvement visualized by means of the roentgen-ray, and I think there is a certain small number of cases in which physical signs of metastases can be elicited before the lesions are of sufficient size or density to cast a distinctive shadow on the plate. The clinician should therefore avail himself of both methods of examination. The examination of the chest will often furnish the indication for taking a roentgen-ray picture, to confirm the presence of metastases and to reveal more accurately perhaps their size, character and location.

Metastases of Breast Carcinoma to Lungs and Pleura. Among the early symptoms which lead one to suspect metastases to the lungs are cough, vague or pleuritic pains in the chest and a feeling of difficulty in getting the breath.

The earliest sign which I have observed is a peculiar limitation of breath sounds, especially marked during inspiration, covering a limited area of the chest. This may or may not be accompanied by fine crackling rales during inspiration, and there may be no dyspnea, no cyanosis, no change in percussion note or fremitus, and no alteration in the vesicular quality of the breath sounds. This limitation of breath sounds, and particularly during inspiration, gives the impression that there is either something preventing normal expansion of lung vesicles, or a thin layer of something obscuring the vesicular murmur. The above signs may be the only ones obtainable and at this stage, the roentgenologist may be entirely unable to confirm the clinician's suspicion of metastases.

In consulting the standard text-books of physical diagnosis one is struck by the fact that almost the only descriptions of physical signs in such cases pertain to well-advanced lesions.

It is important, of course, to rule out other lung conditions, such as the residuum of an old pneumonia or pleurisy, a beginning dry pleurisy and tuberculosis. If any of these conditions are present the difficulties of physical diagnosis (and of roentgenological interpretation as well) are considerably increased. In the absence of a history of pneumonia, pleurisy or tuberculosis, and in the absence of the acute pain usually accompanying a beginning pleurisy, if one has the signs described above in the lower half of the chest, one is much more inclined to suspect metastases than if the same signs were present somewhere in the upper half of the chest, where tuberculosis might be the more probable cause. The signs of metastases are more frequently discovered in the lower half posteriorly than at the apex or anteriorly, because at the apex it is difficult to rule out tuberculosis, and anteriorly the presence of the female breast often obscures the examination of the lung.

Later Signs. With advance of the secondary growths the signs become more marked and more diffuse, so that similar changes may affect a large part of one or both lungs. In addition to the crackling rales, sibilant or sonorous rales may be heard. Later, change in the percussion note and possibly broncho-vesicular or bronchial breathing may be detected. The rales, as the metastases progress, usually increase in loudness and number. There may now be a visible limitation of expansion of the lower thoracic walls (without fluid). Later, pleural effusion may occur and add its characteristic signs to those already mentioned. Dyspnea increases and cyanosis may be marked. The patient may have distressing cough with little or no sputum. Hemoptysis may occur.

Pleural effusion may occur much earlier and may then obscure

all other signs. It may in this way be a source of great diagnostic uncertainty, both to physical examination and the roentgen-ray, particularly in the very late metastases which sometimes occur years after an amputation of the breast. We have found little help in such cases from an examination of the fluid for tumor cells.

In the cases that have recently had an amputation of the breast, and in which one hears when listening over the chest wall at the site of the missing breast a number of crackling rales, it is very difficult to say whether one is dealing with an early pleural metastasis or with a postoperative pleuritis. It is my impression that there is frequently a slight postoperative pleuritis directly beneath the operative field which gives rise to crackling rales that sound as though they were close to the ear.

Metastases to Lungs from Osteogenic Sarcoma. The lungs are almost invariably sooner or later the seat of metastases in this disease. These secondary growths start from cell emboli transported through the blood stream, while in breast carcinoma the route of dissemination is chiefly the lymphatics. As seen on the roentgen-ray plate, they first appear as small round, fairly clean-cut nodules lying within the lung. The symptoms are cough, pain in the chest, and later dyspnea and frequently hemoptysis. These growths when first seen on the roentgen-ray plate may be so small or lying so deeply within the lung parenchyma that no physical signs whatsoever can be obtained, and in these cases reliance for the first detection of metastases, it seems, must be placed on the roentgenological examination, whereas in the case of breast carcinoma metastases the signs may appear before the roentgen-ray findings. It should be borne clearly in mind, however, that these lesions do not become visible on the roentgen-ray plate from the moment of their inception, and that when cough, dyspnea, pain in the chest, hemoptysis or any combination of these symptoms occurs that cannot readily be accounted for by some other lesion, metastases should be suspected even in the absence of physical signs or roentgenological evidence of pulmonary newgrowth.

Later Signs of Metastases of Osteogenic Sarcoma. Later, as the nodules increase in bulk, one obtains various signs, dullness to flatness over some area with crackling and possibly sibilant rales, decreased breath sounds of relatively normal quality or breath sounds changed toward bronchial type. Massive growths may occur which practically obliterate all resonance, breath sounds, fremitus and voice sounds over an entire side or over most of the chest, even in the absence of sufficient fluid to produce such signs. Bulging of a portion of the chest over a massive growth may occur. Retraction of a portion of the chest wall over a secondary lung tumor, which is said to occur sometimes, according to several writers on physical diagnosis, I have never observed. Pleural effusion frequently occurs in these cases, also, and may occur early, so as to mask other signs, both physical and roentgenological.

Mammary Carcinoma: Comparison of Physical Signs with Roentgen-ray Findings. Following is a table comparing physical findings in the chest with roentgen-ray reports in cases of mammary carcinoma. The table includes all of the cases examined personally by the writer from the middle of August, 1920, until about May 1, 1923, with the exception of a good many cases which had to be excluded because of failure to secure the physical examination and the roentgen-ray plate at the same time. There are 216 cases included, of which 7 were men. In all cases the chest examination was made first as part of the routine physical survey, and the roentgen-ray plate was taken later on the same day or within a very few days thereafter. The roentgen-ray plates have been interpreted by Dr. R. E. Herendeen, roentgenologist to the hospital, independently, without any knowledge of the writer's findings. All of these cases have been definitely classified by the breast department as cases of mammary carcinoma clinically, confirmed whenever possible by pathological examination.

TABLE COMPARING PHYSICAL SIGNS WITH ROENTGEN-RAY FINDINGS IN CASES OF MAMMARY CARCINOMA EXAMINED FOR PULMONARY METASTASES.

	Number of cases.	Per cent.
GROUP I.—Physical Signs Indicated Metastases:		
Confirmed by roentgen-ray	18	54.5
Roentgen-ray negative at first; later positive	2	6.1
Roentgen-ray questionable or suspicious	7	21.2
Roentgen-ray negative for metastases	6	18.2
Total	33	100.0
GROUP II.—Physical Examination Questionable or Suspicious of Metastases:		
Roentgen-ray positive for metastases	6	12.3
Roentgen-ray questionable or suspicious	13	26.5
Roentgen-ray negative at first; later positive	4	8.2
Roentgen-ray negative for metastases	26	53.0
Total	49	100.0
GROUP III.—Physical Signs Negative for Metastases:		
Roentgen-ray negative for metastases	107	80.0
Roentgen-ray questionable or suspicious	18	10.4
Roentgen-ray positive for metastases	9	9.6
Total	134	100.0
Grand total	216	

Discussion. In Group I there are 2 cases in which the physical signs were considered positive for metastases, and which were negative to the roentgen-ray at first, but which later showed definite metastases on the plates.

The first of these was patient Mrs. L. L., examined on December 27, 1920, and classified as recurrent inoperable. Her left breast had

been removed three years before and she had received four roentgen-ray treatments two years previously and four or five roentgen-ray treatments the preceding year, the last treatment having been given in September, 1919. The roentgen-ray plate on December 27, 1920, was reported as follows: "Plate does not reveal definite evidence of involvement of pleura, and there is no well-marked evidence of carcinoma metastasis to lungs. The left margin of the gladiolus sterni from second to third ribs seems hazy and irregular and lacking in normal bone density." A biopsy made at this time showed scirrhous carcinoma. On July 19, 1921, seven months later, the roentgen-ray showed "evidence suggesting metastases to lungs," and on September 24, 1921, "characteristic roentgen evidence of carcinoma metastases to lungs." On January 8, 1923, her liver was found to be greatly enlarged, and she died on February 12, 1923.

The second of these cases, Mrs. L. Gl., was examined on July 25, 1921, and classified as recurrent inoperable. The physical examination of the chest indicated the presence of metastases, but the roentgen-ray report was negative. Three months later, on November 1, 1921, the roentgen-ray findings were questionable or suspicious, and eight months later, on March 17, 1922, the roentgen-ray report was positive for metastases. On August 10, 1922, she was found to have a greatly enlarged liver, and she died on November 30, 1922.

Of the cases in Group II, suspected of having metastases as the result of physical examination, 4 were at first reported negative to the roentgen-ray, but later showed positive evidence of metastases on the plates, at intervals of from three and one-half to eight months after the original examination had been made. Three of these cases died in from five to ten months after first coming to the hospital. In one of these cases the only sign demonstrable at the first examination was a diminution of breath sounds at the right base. The remaining case of the four was last seen on March 20, 1923, seven and two-thirds months after her first examination, and was then in good general condition.

The 6 cases just discussed may be regarded as furnishing some evidence, but not proof, that the physical examination detected signs of metastasis of mammary cancer before it could be found on the roentgen-ray plate. It is impossible, of course, to prove that the metastases were present at the time when the physical examination was reported as positive or suspicious, and that they did not develop during the interval of time which elapsed before positive evidence was obtained on the plates; but inasmuch as the signs reported in the beginning in these cases are those found in other cases of known metastases, it seems reasonable to assume that changes were present sufficient to produce physical signs, but not sufficiently marked to cast a distinctive shadow on the plates.

3. Cases in Group I, reported as positive for metastases to physical

signs, in which the roentgen-ray was negative, numbered 6. Of these 3 died, eight months, one year, and fourteen months, respectively, after the first examination. No further roentgen-ray plates had been made. The patient who lived fourteen months was reported by the Social Service Department eight months after the first examination as coughing a great deal. One other patient is probably dead, as she was sent to a home for hopeless cancer cases in September, 1922. She presented an inoperable recurrence. No further plates had been made in this case. The two other cases have been lost track of. Both, however, presented inoperable recurrences. In one of these it seems almost certain that the roentgen-ray failed to show metastases which were present and indicated by physical signs. She first presented herself for examination on October 28, 1921 (Case B. W.). There was no history of any previous lung condition. An inoperable recurrence was present. The physical signs were reported as follows: "Dullness and diminished breath sounds in right axilla and at right base posteriorly. Fine crepitant rales at right base posteriorly. Undoubtedly metastases to pleura or lung." The roentgen-ray report was negative. This has been verified by reinspection of the plate. A biopsy was reported by Dr. James Ewing as carcinoma simplex. The case progressed rapidly, the opposite breast becoming involved. The patient, unfortunately, moved to Massachusetts in May, 1922, and cannot be traced.

Cases in Group II, reported as suspected of having metastases in which the roentgen-ray report was negative numbered 26. Of these 7 died in from three to nine months after their first examination at this hospital. All but 1 of these were classed as inoperable. Three other cases were lost track of so long ago that they are probably dead, and 2 cases were doing badly when last seen, making a total of 12 out of the 26 who are dead, about to die, or probably dead. Two others have been lost track of in the past year. The remaining 12 cases may be said to be in fairly good condition. Unfortunately later roentgen-ray plates of the lungs were made in only 2 of the 26 cases. In each of these the later roentgen-ray report was questionable or suspicious of metastasis. Both cases are living, but probably will soon die, as they were originally classed as inoperable twenty and thirty-one months ago, respectively.

Cases in Group I, in which the physical examination indicated metastases, and in which this diagnosis was confirmed by the roentgen-ray, numbered 18. Further confirmation of the physical examination is given by the fact that 12 of these died in from forty-two days to twenty-one months afterward, several of them having severe cough, dyspnea, pleural effusions and so forth. In 9 of these the record definitely shows that death was due to extension of the carcinoma, with pulmonary, bone or liver metastases. One other case (E. S.) has not been seen since January 31, 1923. She had five later plates made of the chest, which showed definite evidence

of progression in the pulmonary metastases. Case A. P., last seen in September, 1922, complained of pain in her knees, but the roentgen-ray plate was negative for bone involvement. Case H. T., last seen in September, 1922, complained of generalized pains. Case C. L., last seen May 28, 1923, was in poor general condition. Thus, only 2 cases remain out of the 18 who are in good condition. One of these presented an unusual type of breast carcinoma, there being a history of a breast tumor of twenty-five years' duration. Furthermore, only five months have elapsed since these 2 cases first presented themselves for examination.

Cases in Group I, in which the physical signs indicated metastases to the lungs, and in which the roentgen-ray report was questionable or suspicious, numbered 7. Of these 4 died in from three to ten months after their first examination. Of the 3 cases presumably alive, 2 were inoperable, and all 3 have been recently ill with pains suggesting bone metastases. Further plates of the chest had not been made in these cases.

Of the cases in Group II, in which the physical examination was questionable or suspicious of lung metastases, the roentgen-ray report was positive in 6. Of these, 3 died in from nine to ten and one-half months. Of the remaining 3, one, a man, presented an inoperable recurrence, has not been heard from since October, 1922, and is probably dead; another inoperable recurrent case has not been seen since June, 1922, and is probably dead. In the latter case later roentgen-ray plates confirmed the presence of lung metastases, incidentally showing some improvement following high voltage roentgen-ray therapy. The remaining case presented a primary inoperable carcinoma, and is apparently in fairly good general condition at present, seven months after her first visit to the clinic.

Of the cases in Group II, regarded as suspicious for pulmonary metastases from the physical examination, the roentgen-ray report was also suspicious or doubtful in 13. Four of these patients died in from fifty-one days to eleven months after their first visit. Of the remaining 9 cases, 1 is probably dead, 3 have been lost track of, 1 is doing badly, 2 have shown positive evidence of pulmonary metastases on chest plates made five and seven months, respectively, after the initial examination, 1 case showed no change on a plate made three months after her first visit, and only 3 cases are known to be in good general condition.

Contrast with Cases Negative to Physical Examination. The preceding 82 cases were all regarded as positive or suspicious for pulmonary metastases as a result of physical signs obtained, and by their roentgen-ray plates or subsequent course tended to bear out the accuracy of the physical findings in varying degrees. With these I wish to contrast the following 134 cases which were reported as negative for evidence of pulmonary metastasis on physical examination.

The roentgen-ray confirmed this negative report in 107, or 80 per cent. Of these 107 cases, only 31 are recorded as dead or "final" (the term "final" indicating that the case has been lost track of and not necessarily that it is dead). In 15 cases, later roentgen-ray plates, made after an interval of seventeen days to twenty-two months after the first plates, have also been negative. It should be reëmphasized at this point that all the cases included in this report have been definitely classified as cases of mammary carcinoma by the breast service. Three cases showed questionable evidence of lung metastases on roentgen-ray plates made from one to six months after the original negative plates, and 7 of the 107 showed positive evidence of pulmonary metastases on later plates made from two to eight and one-half months afterward. However, in 1 of these cases (A. N.) an opportunity was afforded the writer to examine the chest the day before the roentgen-ray picture was taken, and physical signs of metastases were found and formed the principal reason for having a roentgen-ray plate made.

Of the cases regarded as negative for pulmonary metastases on physical examination, the roentgen-ray reported questionable evidence of metastases in 18 cases, or only 10.4 per cent. Eight of these are dead and 3 others are probably dead. Three showed definitely positive evidence of metastases to the lungs on plates made two to eight months later. Three others were still questionable to the roentgen-ray ten to twenty-three months later, and 2 cases showed less definite evidence to the roentgen-ray three and seventeen months, respectively, after the original questionable plate. Later plates were not made in the other cases of this group.

Of the cases reported as negative to physical examination, with respect to pulmonary involvement, the roentgen-ray report was definitely positive for metastases in only 9 cases in all, or 9.6 per cent of the whole group of cases (Group III) negative to physical examination. Two of these are dead as a result of progress of the disease, 1 has not been heard from since August, 1922, when she was having some pain, and 6 are still in apparently good general condition. Later plates of 3 of the 9 cases (one now dead) confirmed the original roentgen-ray report. An excuse for failing to elicit physical signs in one of these cases may lie in the fact that on the roentgen-ray plate the shadows of the metastases were small, round, discrete, dense areas resembling sarcoma metastases, a quite different picture from the usual appearance of pulmonary metastases of mammary carcinoma. As will be shown below, physical signs of this type of secondary growth are much less readily elicited. This case may possibly represent an instance in which dissemination of mammary cancer took place chiefly through the blood stream, as in sarcoma, rather than through the lymphatics.

Following is a table comparing the findings on physical examination of the chest with the roentgen-ray reports in cases of osteogenic sarcoma. These cases were all examined by the writer between

August, 1920, and May, 1923. Almost an equal number had to be excluded because for one reason or another the physical examination and roentgen-ray examination were not made near enough together for the purposes of this study:

TABLE COMPARING PHYSICAL SIGNS WITH ROENTGEN-RAY FINDINGS IN CASES OF OSTEOGENIC SARCOMA EXAMINED FOR PULMONARY METASTASES.

	Number of cases.	Per cent.
GROUP I.—Physical Examination Indicated Metastases:		
Confirmed by roentgen-ray	2	100.0
Total	2	100.0
GROUP II.—Physical Examination Questionable or Suspicious for Metastases:		
Roentgen-ray negative for metastases	1	
Total	1	
GROUP III.—Physical Examination Negative for Metastases:		
Confirmed by roentgen-ray (negative)	9	75.0
Roentgen-ray positive for metastases	2	16.6
Roentgen-ray positive twenty-one days later	1	8.3
Total	12	100.0
Grand total	15	

Discussion. GROUP I. That the physical examination and roentgen-ray were correct in indicating pulmonary metastases is confirmed in one of these 2 cases by the fact that he lived only forty-eight days after the first examination. The other case disappeared after seven days, but the physical signs and roentgen-ray evidence indicated a large mass in the upper right lobe, and as he has not been seen since August, 1922, it is probably safe to assume that he is dead.

GROUP II. In the single case of this group, three subsequent plates of the chest taken one, two and three months, respectively, after the first examination were also negative. Moreover, a second physical examination of the chest made five days before the last plate was made was also negative; so that the second examination of this case might be added to the following group (Group III) as a negative case confirmed by roentgen-ray. She died five months after the first examination.

GROUP III. Cases negative to physical signs and confirmed by the roentgen-ray numbered 9, or 75 per cent of this group, to which might be added the second physical examination of the single case in Group II, so as to make 10 out of 13 cases confirmed by roentgen-ray, or 76.9 per cent. Of the 9 cases, 7 had later plates made; 5 remained negative to the roentgen-ray for periods of three to fourteen months; of these, 2 died after six months, 2 were lost track of after four and a half and fourteen months of observation.

and 1 is still living after fourteen months, but has recently developed a questionable metatarsal metastasis. One of the 7 cases had a questionable plate four months after the initial examination, and died after eight months and 1 case showed positive evidence of pulmonary metastases after an interval of six months. In this case it is of interest to note that plates made only one and two months previously had been negative. A plate made a month later showed progress of the secondary growths. This patient died after seven and two-thirds months. Of the 2 cases in this group who did not have later plates made, 1 died after four months and 1 was lost track of after six and one-half months, but was then apparently in fair general condition.

In Group III, 2 cases were reported as showing pulmonary metastases on the roentgen-ray plate whose physical examination had been negative. In one of these, a second plate made four months later was negative. Whether this represents a result of treatment, or a spontaneous regression of the tumor, it is not within the province of this paper to discuss. This case was still alive on March 1, 1923, two years and four months after the first examination. The other case had a second plate made after four months, which showed an increase in the secondary tumors. Radiographs of his chest which had been made at Bellevue Hospital had been reported as follows: Negative five months before admission to the Memorial Hospital; positive for metastases four months before admission. He was lost track of in May, 1922.

Case I. S. of Group III, whose last roentgen-ray plate had been negative and who died three months later, was autopsied. Following are the findings pertaining to the chest: "Both lungs are the seat of many marble-sized, well-circumscribed, whitish, sometimes ossified tumors. Opposite the lower dorsal vertebra on the left side is an extrapleural partly ossified metastatic tumor 3 cm. in diameter, about which is a localized pocket of pus 2 cm. in diameter."

Case J. R. of Group III, whose roentgen-ray plate was positive twenty-one days after the physical examination had been reported negative for metastases, also came to autopsy. "On opening the chest, the anterior mediastinum is found filled with moderately hard tumor masses which are densely adherent to the sternum. The pericardium contains a slightly increased amount of fluid. In removing the heart, tumor masses are found attached to the lung side of the pericardium, and at the base of the heart, infiltrating the pericardium in the region of the openings for the large vessels. Both pleural cavities contained about 500 cc of clear fluid. The left lung was adherent at several points, especially at the apex and base, and infiltrated by masses 1 to 10 cm. in diameter. There were 15 to 20 of these which were attached to diaphragm as well as pleura, and some were quite firmly adherent to ribs. The right

lung was almost entirely replaced by tumor masses 1 to 15 cm. adherent to parietal pleura, ribs, and diaphragm." There were metastases also to posterior mediastinum, liver, kidneys and retro-peritoneum.

Summary. 1. It is essential to search carefully for the presence of metastases before planning the treatment of malignant neoplasms.

2. In this paper are described the physical signs of early as well as late stages of metastasis to lungs and pleura in two typical types of malignant neoplasms in which such secondary growths frequently occur: mammary carcinoma serving as an example of carcinoma and osteogenic sarcoma as an example of sarcoma. There are 216 cases of carcinoma of the breast and 15 cases of osteogenic sarcoma reported in the form of tabulated comparisons of the results of physical examination and roentgen-ray examination of the chest for metastases.

3. The earliest physical sign of metastasis to pleura or lung from breast carcinoma is a patchy limitation of breath sounds, particularly during inspiration. This sign may or may not be accompanied by crackling rales or pleural friction rubs. It may be detected in some instances before the roentgenologist is able to demonstrate any shadow distinctive of metastasis. The later signs correspond to those described in text-books of physical diagnosis.

4. The earliest demonstrable physical signs of chest metastases of osteogenic sarcoma may not appear until some time after the roentgen-ray has succeeded in showing the small, round, well circumscribed nodules.

5. A tabulated comparison of the results of physical examination and roentgen-ray findings shows a fairly close agreement. For example, in breast carcinoma, of 33 cases considered positive for chest metastases as a result of physical signs, 27 or 81.8 per cent were to the roentgen-ray either positive at once, positive after an interval, or questionable or suspicious, and only 18.2 per cent were frankly negative to the roentgen-ray.

Of 49 cases which were questionable to physical signs, 23 or 47 per cent were either positive at once to the roentgen-ray, positive after an interval, or questionable, while 26 or 53 per cent were negative.

Of 134 cases considered negative to physical signs, 107 or 80 per cent were negative to the roentgen-ray, 18 or 10.4 per cent questionable, and only 9 or 9.6 per cent frankly positive.

In the small number of cases (15) of bone sarcoma suitable for this study, a similar close agreement was found between physical signs in the chest and the roentgen-ray reports.

6. In cases of cancer of the breast and bone sarcoma, careful physical examination of the chest should always be made in addition to the roentgen-ray examination in order to disclose metastases to lungs or pleura as early as possible.

CHRONIC APPENDICITIS AND ITS DIFFERENTIAL DIAGNOSIS.*

BY I. W. HELD, M.D.,

NEW YORK.

WHEREAS acute appendicitis is in the majority of cases easily diagnosed, chronic appendicitis offers such great difficulty that a detailed discussion of the differential diagnosis needs no apology. Ever since Fitz and Gaston over thirty years ago discovered the important rôle played by the pathological condition of the appendix, the subject has rightly received almost continuous attention.

Acute appendicitis is purely a surgical disease, so much so that the internist but seldom sees such cases at all. Chronic appendicitis, on the other hand, may still be considered a borderline disease, because the symptoms, as will be shown below, are so varied that the patient usually consults the internist long before he does the surgeon, and, because it leads to so many other intra-abdominal complications that even the removal of the appendix may not relieve the symptoms.

Anatomy. For a careful discussion of the differential diagnosis, a brief review of the anatomical peculiarities of the appendix and its pathology is necessary. Anatomically, the appendix presents a small, blind pouch attached to the tip of the cecum. It has the shape of a tube and lies freely in the abdominal cavity. By its vascular and lymphatic supply, as well as by the easy giving way of the walls of the appendix, in disease, and also by the fact that it may spread its noxious influence not only to the immediately neighboring viscera but also to the more distant parts of the body, the pathological appendix is an unusual menace. The length of the appendix varies from 5.5 cm. to the longest which was 28 cm., described by Sonnenburg. It is longer in young individuals than in those of later life. The inner lumen is connected with the cecum by a reduplication of the folds of mucous membrane known as the Gerlach valve. This is, in reality, not a valve at all, as correctly pointed out by Colley, as it contains no muscles and possesses no sphincter action. This so-called Gerlach valve does not prevent the passage of contents from the cecum into the appendix, nor does this structure open in a sphincter-like manner to allow cecal contents to pass into the appendix. Hence the name valve is not correct. Contents passing from the cecum into the appendix and from the appendix into the cecum meet with no hindrance, unless the position of the appendix in relation to the cecum is such that the communication of contents between the two organs is not possible, or unless the connection between the two organs is pathologically obliterated.

* Read before The Eastern Medical Society, December 14, 1923.

Normally the passage of cecal contents into the cecum is quite rapid. Horn found that lycopodium seeds introduced into the colon by means of an enema reach the appendix within fifteen minutes.

Grigorjew was the first to demonstrate roentgenologically that the appendix has peristalsis of its own, and that, depending on its contraction and peristalsis, it changes its position and also its contents, so that normally the appendix will be found to change in contour and also that it is sometimes filled and sometimes empty. This is mentioned here because it is very important in the roentgenological study of the pathologic appendix.

As to whether the appendix is normally filled with fecal matter, opinions differ. Ribberts, in his well-known pathological studies, asserted that a normal appendix is always empty. Klebs, on the other hand, found the appendix filled with feces in 57 per cent of his autopsy material. Aschoff, who paid a great deal of attention to the histological studies of the normal and pathological appendix, came to the conclusion that in 62 per cent of cases the lumen of the normal appendix may contain feces.

Of even greater importance is the fact whether the filled appendix has pathological significance. The roentgenological studies of the appendix have demonstrated beyond doubt, that the normal appendix fills and empties, and also changes its position and contour. Only as the appendix becomes diseased and its elasticity and contractility as well as persistent activity diminish, does it become impossible for it to empty its contents and alter its shape and position. The presence of thick, dried fecal matter and fecal stones in the appendix is, according to the opinion of all pathologists, usually an indication of disease. Such substances may be present in the appendix because the organ has lost its contractile and peristaltic power as a result of inflammation, thereby rendering it unable to rid itself of the fecal contents before being dried out or until a fecal stone forms, as may be the case in acute appendicitis. The fecal material may accumulate in the appendix, become hardened, and form a fecalith, which, in turn, leads to chronic irritation of the appendix and inflammatory changes.

The arterial supply of the appendix is furnished by the ileocolic artery; the blood is carried from the appendix by the ileocolic vein; the latter empties into the mesenteric vein. This is important to remember because, in cases of appendicular disease, the infectious material is at times carried from the ileocolic vein into the mesenteric vein, and so reaches the liver, giving rise to dangerous consequences.

The lymphatics form a network in the submucosa through which they have direct connection with the lymphatic vessels of the mesentery and the peritoneum. They empty partially into the glands lying at the angulus ileocecalis and partially between the layers of the mesentery and its communicating glands. The lymphatic vessels pass from the ascending colon and ileum to the upper surface

of the liver and the ligament connecting it with the diaphragm, and so form a direct communication between the lymphatics of the appendix and of the subphrenic space. There is no lymphatic connection between the female generative organs and the appendix. Affections of the generative organs secondary to appendicitis do not result, as was previously thought via the lymphatics, but by direct extension.

The nerve supply of the appendix is derived from the sympathetic fibers of the mesenteric plexus. The numerous branches and nerves connecting with the nerve fibers of the gastro-intestinal tract explain the fact that the pains which are present in appendicitis may spread over all parts of the abdomen and make the diagnosis of the origin of the pains most difficult. It is of great importance to remember that at times the ileofemoral nerve also connects with the nerves supplying the appendix. This explains why the appendicular pains sometimes extend to the scrotum and to the right thigh.

From the histological standpoint, it is most interesting to note that the appendix has a rich supply of lymph follicles. The lymph follicles are connected with the large lymph vessels, by means of capillaries and the basilar sinus, discovered by Lockwood. From the intestinal lumen the lymph follicles are separated by a thin, epithelial layer which forms small lacunæ in the muscularis mucosa which are very readily destroyed if the appendix becomes infected. Aschoff, who described these lacunæ, found that the areas offer no resistance to the entrance of disease-producing factors and are responsible for the rapid destruction of the rest of the appendix in case of disease. As these lymph follicles are most numerous in the young, it explains the greater frequency of the disease in young people and also why it is more dangerous in early adult life. After twenty or thirty years of age the follicles diminish greatly in number.

The mucous membrane also undergoes atrophy after middle life and may at times disappear, leading to total or partial obliteration of the appendix. The narrowing or occlusion of the lumen, the result of complete atrophy of the mucous membrane of the appendix, is, in the great majority of cases, undoubtedly the result of a previous inflammation which has led to fibrous tissue formation and to complete degeneration of the mucous membrane. Aschoff found in a small number of cases that obliteration of the appendix and complete atrophy of the mucous membrane may exist, however, without any evidence of previously existing inflammation. He showed that before ten years of age the appendix is obliterated in about 66 per cent of cases; up to twenty years of age it is obliterated in 12 per cent; up to thirty years, 20 per cent; after forty years, 28 per cent; after fifty years, 42 per cent; and after sixty years, 14 per cent.

The course of the appendix is usually somewhat curved and runs toward the small pelvis. It possesses its own mesentery, on account

of which it can change its position. The course and position of the appendix depend a great deal on the development of the tip of the cecum. If the cecum is more strongly developed anteriorly and on its outer side, the appendix originates from the median line in front or behind the entrance of the ileum into the cecum. As the course and development of the teniæ determine the form of the tip of the cecum, the position of the appendix depends, on the development of the teniæ, whether they lie below, in front, or behind the ileum. The appendix lies freely in the abdominal cavity and may change its position, lying at times more to the inner side, at times farther below, and at times even above the cecum. The appendix situated in the small pelvis is more exposed to infections and its intimate relation in this position with the intestinal coils makes the appendix dangerous to the intestines, the female generative organs, the urinary bladder and rectum in case of disease. However, in this position encapsulation of a suppurative appendix is more frequent than if it is situated in the ileocecal region, where it has a greater opportunity to rupture into the free peritoneal cavity. If the appendix lies laterally in front, behind, or below the cecum (*laterocecalis*, *retrocecalis*, or *subcecalis*), there is greater protection against the spread of a general peritonitis. Two conditions greatly influence the change in the position of the appendix, namely, the variable position of the cecum proper and the changes in the peritoneum in the region of the appendix. Even under normal conditions the position of the appendix changes depending upon whether it is empty or filled with soft fecal material, or distended with gas. If the appendix is empty it lies behind the small intestine, opposite the anterior superior spine of the ileum. If filled with fluid feces, it drops into the small pelvis. If distended with gas, it even reaches the anterior abdominal wall on a line with Poupart's ligament.

In case of disturbance in the lumen of the colon, and in its transportation of fecal material, the position of the appendix lying either more superficially in the abdomen or lower down in the pelvis, is naturally influenced much more, depending on whether the cecum is filled or empty. Anomalies of the colon and its mesenteric attachment produce dislocation of the appendix of more serious consequences. Such anomalies may be responsible for the abnormal attachment of the appendix. De Quervain showed that if the ascending colon is so situated that it is entirely crowded by the coils of the small intestine the appendix may be pushed behind the cecum (*retroposition*) or to the left side of the abdomen (*sinistroposition*), or to the extreme right of the colon (*dextroposition*). If the cecum is situated very low in the pelvis on account of an abnormally long mesocolon, the appendix may lie on the symphysis and press against the urinary bladder; if, on the other hand, on account of a short mesocolon, there is *dystopia* of the cecum, the appendix may lie

behind the kidney, or close behind, or over the liver. In rare cases, as pointed out by Troell, the ascending colon may be absent and the cecum may begin at the hepatic flexure, in which condition the appendix may be found overlying the transverse colon.

Lane's kink and Jackson's membrane influence the position of the appendix. Cecum mobile and ptosis of the transverse colon may also influence the position of the appendix. The various anomalies in the position of the appendix are mentioned here because they play a most important rôle in the causation of its disease and in the immediate and remote consequences.

The Relation of the Appendix to the Peritoneum. In the majority of cases both the cecum and appendix are covered by peritoneum. Very rarely it may lodge retroceally during embryonic life and be covered by peritoneum only anteriorly. Folds of peritoneum spreading from the cecum to the ileum and from the ileum to the appendix and from the ileum to the peritoneum, may form pockets which serve to limit the mobility of the appendix as well as that of the cecum, and even cause strangulation of the appendix and the cecum. Such folds are not constant. The folds, further, may serve as a protective agent against the spreading of the infection from the appendix to the general peritoneum; on the other hand they may also serve as a bacterial nest.

Pathology and Etiology. The appendix has offered unusual opportunities for pathological study because it has been removed by surgeons during every possible stage. The pathological changes in the chronic appendix vary a great deal. The fact that the chronic appendix is the result of a previously existing acute attack is accepted without question today. Even S. Oberndorfer¹ who, in his excellent pathological studies of the appendix, was at first of the opinion that chronic appendicitis may be present without previous acute inflammation, has conceded the conclusions of Aschoff, that acute appendicitis precedes chronic appendicitis in every case. The reason why the history in so many cases does not reveal the previous acute attack is because, in a great majority of cases, the ordinary stomach ache during childhood was, in reality, as pointed out by H. C. Deaver² and Albu and Rotter,³ acute nonsuppurative appendicitis, from which the patient recovered without operative interference.

As it is now definitely established that chronic appendicitis is never primary, the chronic pathological changes in the appendix depend upon the damage done to the appendix during the acute stage plus the repeated recurrent attacks resulting from the infectious agent lodging in the diseased appendix. In order, therefore, to appreciate the pathological changes that take place in the chronically diseased appendix, a few remarks are necessary about the changes in the acute stage which may lead to chronic changes. In many cases, during the acute attack only the superficial epithelium

of the distal part of the appendix is destroyed. The defect in the epithelium becomes covered with a fibrinous leukocytic exudate and the underlying mucosa and submucosa show fresh leukocytic infiltration.

Such an early stage can only be seen if the appendix is removed within a few hours after the attack. In some areas of the appendix the process may recede during an early stage, leaving no evidence of inflammation. Such are the very mildest cases. As a rule, however, the initial stage progresses into a more complicated one. The infection perforates into the grooves of the mucous membrane and then to the serous membrane of the appendix, where it forms a serous leukocytic exudate and later a fibrinous exudate. Such a stage is termed by Aschoff⁴ "appendicitis phlegmonosa ulcerosa simplex." If this process begins to recede, the superficially destroyed mucous membrane, together with the adhesions of the folds of the mucous membrane, lead to stenosis and occasionally also to atresia, giving rise to the obliterated appendix. The healing of the serous covering of the appendix leads to adhesion of either the appendix to the ileum, cecum, or, depending on the spread of the adhesions and the position and length of the appendix, to even more distant organs (generative organs, urethra, liver, kidney, hepatic flexure, spleen, sigmoid, etc.).

True suppuration, to the point of abscess formation, may take place in the lumen of the appendix and reach the serosa, which, however, becomes so encapsulated by fibrous tissue that it does not give rise to the necessity of immediate surgical intervention but remains the source of chronic irritation. The other forms of termination of acute appendicitis, such as perforation and gangrene, need not be discussed here, as they indicate immediate surgical intervention. One of the other sources of chronic appendicular disease without gross changes in the appendix may be due to the fecal stone lodging in the appendix. The question, whether the fecal stone may exist in a normal appendix or be the result of an infection of the appendix, disabling it from ridding itself of the fluid fecal material and so causing fecal stone is also a matter of considerable discussion. Aschoff holds that fecal stone is usually superimposed upon an infection of the appendix and that it is associated with erosion of the epithelium and, in some cases, even with the destruction of mucous membrane and weakening of the musculature of the appendix. From the clinical standpoint it is important to remember that, although in some appendices the fecal stone may be found postmortem in cases where the history does not point to any appendicular disease, there is no doubt that the fecal stone is an indication of disturbed peristalsis in the appendix and that it is frequently the cause of appendicular colic.

The changes in the chronic appendix, therefore, may be stenosis, induration of the walls of the appendix, retention of mucus, fecal

masses and fecal stones and kinking by means of adhesions. All these changes necessarily give rise to a varied clinical picture. In addition to that, the mesentery of the appendix is also often contracted on account of adhesions which invade the nerves and give rise to considerable pain. The process may extend to the wall of the cecum, causing a moderately contracted and spastic cecum or it may cause catarrh of the mucous membrane of the cecum with dilatation, the so-called typhlatony. At times pathological changes in the appendix may be the cause of diverticuli. From the clinical standpoint it is very important to remember that the appendix may become secondarily invaded as a result of gall-bladder disease or generalized or localized colitis and infection of the female generative organs.

Rheindorf⁵ expressed the opinion that a great many cases of chronic appendicitis are due to worms lodging in the appendix. Of course, a great number of cases in which worms were found in the appendix, have been recorded in literature by surgeons and pathologists, but very few are of the opinion that it is frequently a cause of chronic appendicitis. In this country worms are a very uncommon cause of disease, but there is no doubt that if worms lodge in the appendix, they may give rise to acute and even chronic appendicitis.

Cecil and Bulkley⁶ described a characteristic form of appendicitis, due to parasites, which consists of catarrhal inflammation with small hemorrhages. The subjective symptoms are numerous, the objective symptoms meager. The disease is not rare. Wilson⁷ states that thread worms are frequently the cause of chronic appendicitis and the reason why it is sometimes so difficult to cure thread worms by anthelmintics is because of those that lodge in the appendix.

Some authors have considered that in status lymphaticus the appendix is richer in lymph follicles and is longer and, hence, more frequently the seat of disease. That the appendix is in reality longer in individuals with status thymico-lymphaticus cannot be denied. It is due to the fact that these individuals are usually tall and thin and all the organs are longer and narrower, but that these are more likely to be afflicted with appendicitis than others is not proven. It is quite likely, however, that individuals of such status, if afflicted, are prone to have more symptoms as they are physically inferior and hypersensitive.

Tuberculosis, actinomycosis and carcinoma may affect the appendix without affecting other organs in the body. Actinomycosis, if it affects the appendix, is usually secondary to actinomycosis elsewhere in the body. It may also be stated that at times mucus cysts are found in the appendix and its mesentery. Such cysts have been named pseudomyoma. They may form a tumor of considerable size, or their gelatinous contents may break through the appendix into the peritoneum, or at times undergo malignant degeneration.

Maresch⁸ found distinct neuromas in a number of obliterated

appendices which he attributes to the plexus of the submucosa becoming involved by fibrous tissue, which results in the process of healing of the ulceration in the mucous membrane of the appendix. Such neuromas may give rise to a great deal of pain and are, therefore, of clinical interest. It is analogous to the neuroma associated with ulcer of the stomach, to which Störck called attention.

Symptoms. The symptoms of chronic appendicitis may be so pronounced as to offer no difficulty whatever. This is true of the cases in which a history of one or repeated attacks of acute appendicitis is present, or in which pains of varying severity exist over the ileocecal region, either coming on periodically or of a persistent nature. This is, however, only true of the minority of cases. In the greater number of cases, the symptoms are very vague and, hence, offer great difficulty in diagnosis. In the majority of cases there is no definite history of an acute attack, either because such an attack existed during childhood, and, therefore, cannot be recalled by the patient, or because the acute inflammation gave rise to such insignificant symptoms as to be hardly noticeable. This is one important reason why there is so much difference of opinion as to whether vague gastric symptoms with spontaneous pain in the ileocecal region and tenderness should be attributed to chronic appendicitis or to some other cause. There are so many causes for pain in the ileocecal region with gastro-intestinal symptoms that the mere complaint of gastric distress and tenderness in the ileocecal region by no means justifies the rash conclusion that chronic appendicitis is the cause of it. Until ten or fifteen years ago surgeons and internists were ready to yield to the temptation, to consider it chronic appendicitis and advise operation, if the patient complained of pain in the ileocecal region and had gastric symptoms. The numerous disappointments, however, in which the removal of the appendix, even if the pathologist pronounced it diseased, brought no permanent relief, have rightly taught us to be more careful before we attribute the symptoms to chronic appendicitis.

The general recognition that a diseased appendix may produce definite symptoms of gastric and duodenal disorder with few or no localizing symptoms, is due to the study of the pathology in the living. Especial credit must be given to Moynihan,⁹ the Mayos, Paterson and Fenwick. Moynihan has rightly termed these symptoms, "appendicular dyspepsia," a term accepted by men like Deaver, the Mayos, Lichty¹⁰ and others.

Sir Humphrey Rolleston¹¹ divided correctly the symptoms into four groups: 1, Reflex; 2, mechanical; 3, toxic; 4, infective. This division corresponds so much to facts that it seems advisable to elaborate on it even more fully than is done in the original article by Rolleston. The question will at once suggest itself whether it is possible to judge the pathological changes in the appendix from

one of the four groups of symptoms. This is only possible to a very limited degree and mainly regarding the mechanical and infective groups of symptoms.

1. *Reflex.* According to Rolleston, to the reflex symptoms of chronic appendicitis belong those complaints which are characterized by hypertonus and spasm of the stomach, as well as failure to relax on the part of the pyloric or ileocecal sphincter, leading to gastric or ileal stasis, and so to excess of acid or to toxemia. That hypertonus and hyperperistalsis are often reflexly caused by the diseased appendix, and are responsible for the symptoms, is proved by the fact that Moynihan observed violent gastric contractions and spasm of the pylorus or other parts of the stomach in the presence of a chronically diseased appendix on the operating table, in cases of chronic appendicitis. Hurst¹² observed fluoroscopically spasm of the greater curvature if pressure is exercised over the ileocecal region. The same author also states that the delay in the ileum encountered in chronic appendicitis is due to spasm of the ileocecal sphincter.

The symptoms enumerated by Rolleston and the observations of Hurst indicate disturbed motor phenomena in the stomach and ileum, the result of chronic appendicitis. The disturbance in the motility of the colon, bringing about marked spasm of different parts of the colon, are also frequently associated with chronic appendicitis, thus explaining spastic constipation and sometimes the marked pain over the sigmoid. Chronic appendicitis does not always disturb the motor function in the gastro-intestinal tract and bring about hypertonus but it may also cause loss of tone in different parts of the gastro-intestinal tract. It is, therefore, no wonder that in a certain number of cases there is gastric atony which is responsible for most of the symptoms, or atony of the cecum (typhlatony) may be present. In these cases the atonic type of constipation is encountered, or, as is more rarely the case, constipation alternating with diarrhea. Very frequently there may be symptoms of hypertonus and spasm in some parts of the gastro-intestinal tract and loss of tone in other parts. It has been my experience that in chronic appendicitis there is often atony of the stomach and spasticity of the cecum or descending colon.

The sensory phenomena due to chronic appendicitis manifest themselves largely by the presence of pain in the epigastric region. The cause of reflex pain has given rise to some discussion. Sir James MacKenzie¹³ maintains that it is referred to the peripheral termination of the sixth and seventh dorsal nerves in the abdominal wall, and that this depends upon the irritated focus in the spinal cord. Hurst argues that the pain is visceral in the pyloric end of the stomach and due to peristalsis. They agree, however, that the epigastric tenderness is due, not to pressure on the stomach, but to the irritated focus in the spinal cord which causes an exaggerated sensory

effect when the skin and especially the muscles of the underlying subperitoneal tissues are pressed upon. That the reflex pain is due to irritated focus of the spinal cord is evidenced by the fact that in certain cases of chronic appendicitis, the pain may be thoracic, even simulating stenocardia, if the irritating center is situated higher in the spinal cord, in the fourth or fifth dorsal nerves. The pain may also radiate down to the urinary bladder or even to the right thigh, simulating cystitis or sciatica, not due primarily to pressure on the nerves, as is often the case if the symptoms are of a mechanical nature, but due to the fact that the irritating center is lower in the spinal cord (last dorsal or lumbar nerves).

Reflex secretory phenomena resulting from chronic appendicitis are manifested in the majority of cases by disturbances in gastric secretions. In most cases there is hypersecretion and hyperacidity, which is chiefly of alimentary character. In a lesser number of cases there may be transient continuous hypersecretion. Lowered acidity in chronic appendicitis is much rarer. The reflex secretory disturbances may exert their influence upon the colon, giving rise to colica mucosa with the accompanying periodic attacks of cramps and the discharge of large quantities of mucous casts, or it may even spread to the salivary secretions causing increased salivation. In some cases it may influence the secretion of urine, giving rise to frequent urination. This, however, seems more likely to be the result of gastric hyperacidity with either diminished acid in the urine or even alkalinity of the urine which causes irritation of the urinary bladder and frequency in micturition, but no real increase in the quantity of urine. The transient increased hypersecretion in the colon may give rise to frequent attacks of serous diarrhea.

The reflex symptoms are not always alike in all cases of chronic appendicitis and they are not always alike even in the same individuals. In some the motor phenomena predominate, bringing about distress in the epigastrium and epigastric pressure soon after meals, persistent belching, regurgitation of sour fluid, peristaltic unrest in the upper quadrant of the abdomen and the different parts of the colon, especially in the cecum, rigidity of the cecum and even rigidity of the rectus overlying the cecum. Where there is a depression in the motor function of the gastro-intestinal tract, the symptoms of gastro-intestinal atony are encountered, consisting of sensation of persistent heaviness in the abdomen, the splashing sound over the stomach and cecum and other signs of atony in the cecum, such as gurgling which is persistent most of the time, and especially marked five or six hours after meals.

In other cases the sensory disturbances predominate. Such patients complain of pain out of proportion to all the other findings. The pain, as already stated above, may be epigastric or may even be thoracic, but what is very characteristic of the pain is the fact that, as was pointed out by Aaron, pressure over the appen-

dicular region brings about the pain in the area of which the patient spontaneously complains. Head's zone is also most marked over the appendicular region.

Where the secretory phenomena predominate there is marked pyrosis, regurgitation of acid secretion and sometimes even vomiting. The secretory type may sometimes simulate gastric or duodenal ulcer and makes the differential diagnosis clinically impossible. In reality it is not unlikely that the persistent hypersecretion leads to superficial gastric erosions and gastric symptoms, or even gastric or duodenal ulcer, which may heal upon the removal of the appendix. That this is so is verified by the studies of Roessle,¹⁴ who brought pathological proof that ulcer of the stomach or duodenum is not infrequently the result of chronic appendicitis.

A number of other symptom-complexes have been attributed to chronic appendicitis which may also be considered of a reflex nature. The French School speaks of "appendicitis asthmatique," "appendicitis epileptique," "appendicitis cephalique," "appendicitis neurasthenique;" and "appendicitis hysterique." Of course, such cases are rather rare, but they are undoubtedly encountered. That chronic appendicitis may sometimes be reflexly responsible for the most peculiar symptoms is illustrated by the following case:

CASE I.—A woman, aged twenty-eight years, referred by Dr. J. J. Rosenberg, was subject to periodic attacks of oppression in the chest and hoarseness to the extent of almost complete aphonia. The physical examination of the chest was entirely negative. In view of the fact that the patient gave a history of having suffered occasionally from abdominal cramps, her family physician, insisted that a complete gastro-intestinal examination, including roentgenography, should be made. This examination disclosed evidence of marked adhesions in the ileocecal region with an abnormally situated elongated and persistently filled appendix, which was tender. Because of her protracted suffering, she herself insisted upon operation. Dr. A. A. Berg removed a severely diseased appendix. Several years have now elapsed since the operation and the patient has had no return of her symptoms.

The question now arises: Why does chronic appendicitis in a certain number of cases give rise to reflex symptoms and why do the reflex symptoms differ in different individuals and sometimes in the same individual? The answer to this question may lie in the fact that these individuals are primarily afflicted with disturbances in the vegetative nervous system. In most of these sufferers all or some of the following symptoms may be encountered: the patient is usually of tall, frail stature, with long neck, long, flat thorax, floating tenth rib, poorly developed musculature and enteroptosis with infantilism of the genital organs. The objective signs are: glistening, prominent eyes, wide lids, hypertrophied follicles at the

base of the tongue, moist cold hands and also cold feet; dermagraphy is present, the pulse is as a rule slow, salivation is increased and there may be lachrymation. In other words, they are afflicted with some or all of the symptoms which, according to Eppinger and Hess,¹⁵ are the expression of vagotonia. Pure vagotonia is, however, very rare. In most individuals with disturbance of the vegetative nervous system there are both vagotonic and sympathicotonic symptoms. In a patient afflicted with disturbances in the autonomic nervous system suffering from appendicitis, no matter what the pathological changes in the appendix may be, the reflex disturbances caused by the hypersensitiveness of such an individual are much more pronounced than the local symptoms. This is the reason why it is so difficult to differentiate purely functional symptoms with stigmata in the vegetative nervous system from those of an organic disease aggravated and masked by the symptoms caused by the unbalanced autonomic nervous system.

In these hypersensitive individuals, the local disturbance of the appendix may be very insignificant and still cause very unusual symptoms. On opening the abdomen, a small obliterated appendix or, on incising the appendix small erosions of the mucous membrane may be found, or the appendix may be found to be filled only with fecal stones and mucus and one may wonder why such insignificant pathological changes in the appendix should have caused such an array of symptoms.

This group of cases offers great difficulty in the differential diagnosis. If the diagnosis is made, the frequent question arises, whether the removal of the appendix will actually remove the symptoms. In reality, the removal of the appendix may only do away with the symptoms for a short time and this is the reason why controversy has resulted as to whether appendicitis with mild local symptoms and marked reflex disturbances should be considered a surgical disease. If, however, the fact that any local affection often aggravates the symptoms caused by an unbalanced nervous system is taken into consideration, it becomes evident that it is not at all unwise to remove the disturbing cause. Permanent favorable results can only be obtained if proper attention is also paid to the congenitally inferior autonomic nervous system.

2. *Mechanical.* The mechanical symptom-complex may be caused by two factors: (a) by the presence of foreign bodies in the lumen of the appendix proper, and (b) by appendicular adhesions to the neighboring organs.

(a) To the former belong the cases in which fecaliths or parasites are lodged in the appendix. There has been considerable discussion as to whether the substances named above can be responsible for chronic appendicitis. In agreement with Aschoff, it may be stated that primarily they would not cause symptoms, but in the presence of ulceration in the appendix or other chronic inflam-

matory changes within the lumen of the appendix, these foreign bodies may give rise to repeated attacks of appendicular colic or even persistent discomfort in the ileocecal region. Foreign bodies, such as stones, worms or seed lying in a healthy appendix may cause no symptoms at all or at most only mild attacks of transient pain in the ileocecal region.

It has already been mentioned above that intestinal worms are considered by some to be a very important factor in the causation of acute and chronic appendicitis. Their importance as a primary cause is very doubtful but if worms are present in a diseased appendix, they may give rise not only to the symptoms of chronic appendicitis but also to the annoying symptoms characteristic of intestinal parasites such as nausea and excessive appetite. The patient has a sallow face, and there is an increase of eosinophiles in the blood. Worms in the appendix may sometimes explain why, even after complete elimination of the worms from the intestines, the symptoms still persist. A case of this character observed by me was operated upon by Benjamin T. Tilton in Har Moriah Hospital.

(b) The second group causing mechanical symptoms is the one due to adhesions, and this is by far the most important. The symptoms in these cases depend considerably upon the extent of the adhesions. In most cases, adhesions usually spread to the cecum, causing perityphlitis. Such patients usually complain of fulness in the cecal region and pain of varying severity. The abdominal wall over the region of the cecum is usually tender and quite often the Bastedo sign (inflation of the rectum, causing pain over McBurney's point), or the sign pointed out by Reder (digital examination of the rectum causing pain over the McBurney's point), is present in these cases. Adhesions between the ileum and cecum often cause pain in the left hypochondrium, the result of ileocecal valve incompetency (Cole). Sometimes adhesions extend into the right hypochondrium, causing traction and kinking of the hepatic flexure, or they may often spread to the liver and gall-bladder, simulating biliary disease and giving rise to moderate subicteric discoloration of the sclera, increased bilirubin in the blood serum, and, transiently, even show the presence of a small quantity of bile in the urine. The adhesions may also spread to the lumbar region, causing pressure on the ureter, simulating renal or ureteral colic, and may even cause the appearance of red blood cells in the urine or sometimes even hematuria. Cases are mentioned in literature where the adhesions have caused pressure on the sciatic nerve, resulting in persistent sciatica which disappeared entirely after the removal of the diseased appendix.

Chandler¹⁶ mentions a case of an enlarged chronically inflamed appendix, the lumen of which contained pus, and which caused pain and hyperesthesia and weakness in the left limb, circumscribed

pressure pain over the fourth lumbar vertebra and severe paroxysmal pain over the lumbar region.

The adhesions may spread to the female generative organs, leading even to sterility.

The adhesions may sometimes give rise to the formation of dense bands, causing kinking of the cecum and pulling of the cecum downward to the symphysis, or, what is more common, a pulling of the cecum upward and backward. The bands may sometimes spread from the ileum to the cecum, causing a distinct Lane's kink, or they may encircle the cecum, giving rise to intermittent progressive intestinal obstruction. In these cases, the symptoms are those of chronic intestinal obstruction. Constipation becomes obstinate; even laxatives and enemas have but little effect. Sometimes transient diarrhea may be present, which may be due to the catarrh of the colon caused by the scybalous feces or the diarrhea may be the result of the fluid stool passing through, whereas the solid feces stagnate. Such patients have a moderately distended abdomen, are often nauseated, and have frequent attacks of colicky pains due to peristaltic unrest. In severe degrees of obstruction there may be continuous rumbling in the colon. Dense adhesions in the ileocecal region may cause the patient pain if he lies on the left side. In some cases the adhesions cause contraction of the cecum, and if the cecum becomes distended with gas there is invariably pain. Such patients are usually very uncomfortable when constipated. In other cases the adhesions cause distention in the cecum, and these patients are more comfortable when constipated, because after evacuation of the bowel the cecum collapses, causing traction on the peritoneal bands.

At times the adhesions around the appendix may give rise to a distinct palpable mass, simulating a tumor in the ileocecal region. In these cases, the differential diagnosis between ileocecal tuberculosis, primary tuberculosis of the appendix, and primary carcinoma of the appendix, as well as actinomycosis of the appendix, comes into consideration. Primary tuberculosis and primary carcinoma of the appendix are diagnosed only upon the operating table. There is hardly a case on record where the diagnosis was made before operation. The diagnosis of ileocecal tuberculosis will be discussed in connection with the roentgen-ray diagnosis of chronic appendicitis. Actinomycosis of the appendix is rare. It is characterized by its chronicity, by the fact that the skin overlying the appendicular region becomes adherent to the abdominal wall, and by the presence of actinomycosis elsewhere in the body. The objective diagnostic signs of chronic appendicitis resulting from adhesions are best disclosed by the roentgenography, which will be discussed later.

3. *Toxic.* Rolleston states that the absorption of bacterial toxins from the appendix may set up general toxemia and even cause

myocarditis, and damage to the mucous membrane in the stomach and intestines, and thus give rise to hemorrhage. To what extent toxic absorption from the diseased appendix may give rise to general toxemia it is very hard to tell. The fact, however, that chronic appendicitis sometimes gives rise to severe gastric hemorrhage (parenchymatous hemorrhage—Dieulafoy) must be strongly emphasized. Fenwick¹⁷ assumes the hemorrhage to be of toxic nature. Soltan believes that the hemorrhage is due to the fact that the gastric mucosa is penetrated by protracted hypersecretion and hyperacidity to the point of erosions of the stomach. This is, however, very doubtful. Whether the hemorrhage is of toxic nature or not cannot be stated with certainty. The 3 cases of gastric hemorrhage the result of chronic appendicitis observed by the author, all of which were operated upon, seem to indicate that the bleeding is, in reality, more of hemolytic origin (caused by toxins) than of any other known source. The hemorrhage is profuse, its control difficult, it has no tendency to respond to treatment, and there is a rapidly developing anemia.

To the toxic symptoms may also be added those symptoms of chronic appendicitis which simulate endocrine disturbances, especially hyperthyroidism. Much more rarely may chronic appendicitis simulate Addison's disease. A case of this nature was seen by the author and deserves brief mention.

CASE II.—A woman, aged thirty-four years, a mother of three healthy children, gave a history of two definite attacks of acute appendicitis six years before. She came with symptoms of severe asthenia, marked loss of weight, dark skin, and also discoloration of the mucous membrane of the mouth. The blood-pressure was very low, and vomiting was very marked. She had an increased tolerance to sugar. The case, therefore, had all the earmarks of Addison's disease. In view of the fact, however, that she also had severe tenderness in the ileocecal region with marked resistance and a suspicion of a palpable mass, the gastro-intestinal tract was roentgenographed. It showed marked ileocecal stasis and incompetency of the ileocecal valve. Because of the extreme asthenia and secondary anemia, the patient was transfused twice and after slight improvement an operation was advised. She was operated on by Dr. A. A. Berg. Extensive adhesions in the ileocecal region and a very thick and enlarged appendix were found, the lumen of which was filled with pus. Convalescence was rather stormy. The patient was in collapse after the operation for several days, but active stimulation, continued Murphy's drip, and a third transfusion made the patient rally and eventually she recovered completely.

4. *Infective.* That microorganisms, especially streptococci, lodging in a diseased appendix, may give rise to symptoms of mild infection is not surprising. The microorganisms may spread to the

neighboring organs, and cause chronic pyelitis or they may spread to the gall-bladder causing chronic cholecystitis. Rolleston states that chronic bacterial infection of the appendix may give rise to small pulmonary emboli and pleurisy and local thrombophlebitis of the iliac veins. The symptoms of the infective group are: tiredness, moderate elevation of temperature especially after exercise, chilliness, and increased pulse frequency. The symptoms may even simulate pulmonary tuberculosis. Schnitzler¹⁸ states that pulmonary tuberculosis often leads to symptoms simulating chronic appendicitis without any local changes in the appendix. In expressing this opinion he takes the stand exactly opposite to that of some of the French surgeons, who state that chronic appendicitis may often give rise to symptoms simulating pulmonary tuberculosis, and the removal of the appendix causes a disappearance of the symptoms. The view of the French School would appear to be the sounder one.

Diagnosis. In the diagnosis of chronic appendicitis, the history of one or more acute attacks plays a very important rôle. In the absence of such a history, the diagnosis become difficult. From the symptoms alone it is hard to make a diagnosis. As to the objective findings, the following are of importance:

(a) Tenderness in the ileocecal region.

(b) Rigidity over the right rectus muscle is present even in some chronic cases, as rightly pointed out by Ransohoff.¹⁹ This is especially marked if there are adhesions around the cecum.

(c) The diagnostic value of gastric secretions in chronic appendicitis is estimated differently by different authors. Fenwick states that if there is ulceration in the mucous membrane of the appendix there is usually hyperacidity. If chronic appendicitis is complicated by adhesions there is usually subacidity. According to our experience, chronic appendicitis is much more often associated with hyperacidity than with subacidity, irrespective whether it is complicated by adhesions or not.

(d) Aaron's sign: pressure in the appendicular region causing pain in the epigastrium.

(e) Bastedo sign: tenderness over the ileocecal region on inflation of the colon. This is present in a limited number of cases, and chiefly in those in which chronic appendicitis is complicated by adhesions.

(f) Tenderness over the appendicular region on the administration of an enema, likewise rare.

(g) The Reder sign: tenderness over the appendicular region upon rectal examination, also very rare.

(h) Rovsing's sign: pain over the appendicular region if pressure is exercised over the left side at a point corresponding to the McBurney's point on the right side.

It was observed by the author that in case of retrocecal appendi-

citis the pain, although persistent over the right loin if pressure is exerted there, is referred to the appendicular region.

Roentgenography. Much importance must be attached to the roentgenography in the diagnosis of chronic appendicitis, and, hence, a few remarks about the roentgenological appearance of the normal cecum and appendix may be in order, to have a proper understanding of the pathology.

Normally, the contrast meal reaches the cecum two to four hours after the ingestion of the meal, and the last remains of the meal leave the small intestines after eight to nine hours. The normal cecum, as well as the ascending colon, do not show deep segmentations. The segmentations are only about half as deep as the haustra of the transverse colon. The cecum is about 7 cm. long and is separated from the ascending colon by the tenia mesocolica. This boundary, however, cannot be seen, as a rule, on the skiagraph unless the habenula caeci which form these tenia are especially marked. Normally, about half of the cecum is situated in the right iliac fossa. If the cecum moves almost to the median line when the patient is turned on his left side, one may speak of cecum mobile. This is mentioned because, according to Wilms, it plays an important rôle in the differential diagnosis, as it gives rise to symptoms simulating chronic appendicitis.

The lowest point of the cecum when the patient is in an upright position lies about one or two finger breadths above the center of the acetabulum. Because the mesentery of the cecum is longer, it is more or less freely movable upward and downward.

Until 1911, it was assumed that the appendix could not be visualized roentgenologically. It is probably due to the fact that the earlier work was done by means of the Rieder contrast meal. When the thin meal, especially buttermilk suspension, was introduced, the visualization of the appendix became common. The first to have described the appendix roentgenologically were Quimby,²⁰ Case,²¹ Imboden,²² Eisen,²³ Cohn,²⁴ Hurst,²⁵ Groedel,²⁶ as well as Schwartz, Stierlin, and others.

There has been a great deal of discussion as to whether the filling or the nonfilling of the appendix with the contrast indicates disease. There is almost universal agreement today that no conclusion as to its pathology can be drawn from the filling or nonfilling of the appendix. Some assert that early in life, up to the age of about twenty years or even thirty, if the appendix does not fill it indicates disease, whereas beyond forty the normal appendix should be obliterated, and, therefore, if it fills, it indicates disease, but since such assertions do not correspond to facts, they have no clinical or diagnostic value.

The position and the length of the normal appendix varies considerably in different cases and at different times, which definitely shows that the appendix has independent motility and mobility. This is important because if the appendix manifests the same shape and position

persistently it is an indication that it is fixed by adhesions. Besides the motility of the appendix in toto at its mesenterium, definite peristaltic contractions in the wall of the appendix may be seen, which often make the appendix appear separated into different portions. Cohn, and, later, Grigorieff, were the first to point out the fact that the appendix may fill and empty repeatedly if the patient is studied periodically while the contrast meal traverses the entire gastro-intestinal tract. This can absolutely be confirmed.

Because of the importance of the competency of the ileocecal valve in the diagnosis of chronic appendicitis and other lesions in the ileocecal region, a few remarks must be made on this subject. Case,²⁷ Dietlin and Groedel were the first to attribute clinical importance to ileocecal valve incompetency. Case began his observations in 1910. He found the valve to be incompetent in about one-sixth of all cases examined with the enema. For the most part the patients examined were suffering from gastro-intestinal symptoms and those of complications of constipation. Dietlin believes that the valve is usually competent in children and adults, and incompetent in infants. Incompetency is generally an indication of disease in the iliac region. The work of Keith, and later of Rutherford, proves that the ileocecal valve is normally competent. Carman states that the enema enters the ileum in the greater majority of cases, probably about nine-tenths. The patients examined are of the character usually sent for roentgenography test; they complain of gastro-intestinal symptoms of some sort. But there are also a considerable number whose symptoms are found on operation to be due to other abdominal disease, not affecting the bowel, which is found normal. Carman found of all degrees incompetency ranging from trivial backflow from the valve to an extensive filling of the lower ileum, without any relation between this insufficiency and the pathological condition of the ileocecal region being noticeable.

For the roentgenological study of the diseased appendix, both the direct and the indirect signs must be utilized. The value of the direct signs was most carefully studied by Spriggs and Marxer²⁸ and, according to them, in order to determine directly whether the appendix is diseased or not, one must pay attention to the filling and emptying of the appendix, its shape, mobility, position, hyperactivity, spasm, tenderness, and the presence of concretions. In order not to miss the direct visualization of the appendix, the patient must be examined fluoroscopically and the appendix should be palpated under the fluoroscope after six, eight, twenty-four, forty-eight and seventy-two hours, and sometimes even beyond that time after the cecum is entirely empty, in order not to overlook a retroceally situated appendix. The normal appendix may empty and fill repeatedly during the course of the examination by means of the contrast meal. If the appendix remains persistently filled after the entire gastro-intestinal tract is empty, there is reason to attribute to it a pathological significance.

As to the shape, the abnormal appendix may sometimes be short and thick, sometimes almost as wide as it is long, the shape and position not altering throughout the entire course of the examination. The shortness and thickness do not necessarily indicate that the diseased appendix is not longer than what is seen on the roentgenogram, but it does indicate that the lumen of the appendix is obliterated in its center, and, therefore, only the upper part fills with contrast substance. The appendix may be unusually long, thick and persistently filled.

The position of the appendix varies even physiologically, and a malposition of the appendix is of pathological importance only if the appendix is at the same time fixed and tender. Certain malpositions of the appendix, however, invariably indicate pathology, and these are: if the appendix is pulled to the left side, or pulled low down into the pelvis, or to the region of the urinary bladder, or up to the retrocecal region.

Tenderness over the appendicular region, fluoroscopically observed and when persistently present, is of great diagnostic significance. The presence of concretions indicates disease only if other symptoms and signs of chronic appendicitis are present. If the appendix is persistently kinked and does not alter its position, it is likewise an indication of disease.

The other direct signs are the result of the adhesions caused by the diseased appendix. These are: either a very low or very high position of the cecum, restricted mobility of the cecum, pulling of the sigmoid to the right or pulling of the cecum to the left, sometimes traction and pulling of the transverse colon downward, and kinking of the hepatic flexure.

If the adhesions are such as to cause matting of the ileum with the cecum, there is marked delay in the emptying of the ileum, even beyond twenty-four hours. The traction of the adhesions on the ileocecal valve causes it to become patulous, resulting in ileocecal valve incompetency. Very frequently there is gas in the lower ileum on account of ileocecal adhesions.

The indirect roentgen-ray signs of chronic appendicitis in the sequence of frequency are: ileal stasis not due to adhesions, but the result of spasm of the ileocecal valve (Hurst); ileocecal valve incompetency, due to failure of the ileocecal valve to close; stasis in the cecum after the entire colon is empty; spasticity or atony of the cecum, spasm in the pylorus, and, finally, spasm of the greater curvature of the stomach if pressure is exercised on the appendicular region (Hurst). The last is a very rare finding, according to my experience, but it may be present in vagatoniacs afflicted with chronic appendicitis. At times enterospasm or spasm of the descending colon is associated with chronic appendicitis.

Very rare indirect roentgenological signs are marked paralysis of the cecum (typhlatony) or a very movable cecum.

The gastric motility in chronic appendicitis varies a great deal, depending entirely upon the tone of the stomach. Spasm of the pylorus or of the sphincter pylori in chronic appendicitis causes, as a rule, no delay in the emptying of the stomach. If there is considerable gastric atony in connection with chronic appendicitis, there may be marked delay in the emptying of the stomach.

Differential Diagnosis. From the diagnostic, as well as from the therapeutic, standpoint, it seems most practical to discuss the differential diagnosis under the following divisions: (1) Diseases which simulate chronic appendicitis, the appendix being normal; (2) diseases resulting from chronic appendicitis; (3) where the primary disease had its starting point in another intra-abdominal viscus, eventually affecting also the appendix.

To the first group belong the following diseases: Hysteria, as well as neurasthenia, which may cause persistent pain in the ileocecal region with gastro-intestinal symptoms of varying intensity. Such cases are very trying, and only too often they are submitted to surgical intervention, the operation disclosing a normal appendix. Hysterical individuals may even lose all their symptoms after the removal of the appendix, these being purely the result of psychologic influence. Neurasthenic individuals, on the other hand, with general atony of the gastro-intestinal tract and typhlatony in particular, remain with the same symptoms after the removal of the appendix.

The differential diagnosis between hysteria and neuresthenia with appendicular symptoms (pseudo-appendicitis) and that of true chronic appendicitis is often impossible. Therefore, in all neuropathic individuals hysterical stigmata should be carefully looked for. In neuresthenics marked atony of the cecum does not cause any rigidity in the ileocecal region, but makes the cecum feel rather doughy upon palpation and there is, in most cases, gurgling in the cecum. The roentgen-ray examination shows an unusually dilated cecum filled with gas and sometimes even fluid.

Another functional disease which frequently simulates chronic appendicitis is enterospasm, either of the entire colon, or only parts of the colon. This has been particularly pointed out by Lieck.²⁹ If the spasm involves the entire colon, whether due to lead poisoning, tabes dorsalis, intestinal parasites, chronic colitis, or enteritis membranacea, or whether of functional origin, as in colica mucosa or pure vagotonia, there is usually no difficulty in the differential diagnosis. If, on the other hand, the spasm is confined to the cecum, whether due to typhlitis or of a functional nature, the diagnosis is very difficult and quite often impossible.

Some differentiating points may assist in arriving at a proper diagnosis. Spasm of the cecum, the result of typhlitis, often causes most discomfort if the patient partakes of an excess of vegetables. The pain is usually most marked four to six hours after a meal,

at the time when the food reaches the cecum. Spasm of the cecum of a functional nature causes persistent pain, and, on careful palpation, one may succeed in outlining the rigid cecum. Roentgenological examination is of great value in these cases, showing as it does, the haustra of the cecum very plainly. Normally, the cecum does not show these haustrations. Here, the cecum, instead of being about twice the width of the descending colon, as in normal cases, is as narrow as the descending colon, or even narrower. The spasm of the cecum interferes with the contrast enema completely filling out the cecum, and sometimes it may not fill in at all. In other words, delay in retroperistalsis is very prolonged. The contrast taken by the mouth shows small spots of barium in the contracted cecum sometimes for days after the entire colon is empty.

The movable cecum (cecum mobile—Wilms) may simulate chronic appendicitis. This, however, is generally associated with general loss of tone and unusual mobility of the other abdominal organs. If the patient is examined fluoroscopically while lying on the left side, the cecum is seen to move two or three fingers' breadth to the left of the median line. Of course, spasm and atony of the cecum, as well as cecum mobile, may be secondary to chronic appendicitis.

Another disease which may be classified as functional and sometimes simulates chronic appendicitis is the movable or floating right kidney. This may give rise to appendicular pain, but a careful examiner will hardly have any difficulty in making the differential diagnosis.

Of the organic diseases of the cecum, giving rise to difficulty in the diagnosis, the following are to be considered: tuberculosis, carcinoma and actinomycosis of the cecum and ileocecal tuberculosis. Tuberculosis of the cecum and ileocecal tuberculosis are usually associated with tuberculosis elsewhere in the body, and the roentgenological examination, as first brought out by the studies of Stierlin³⁰ and, later, by Brown and Sampson,³¹ offers considerable aid in differential diagnosis.

The cecum and ascending colon fail to hold the contrast substance or only do so partially, and, hence, the cecum may not be visualized at all or only in the form of a narrow, partially filled spastic tube throughout the entire course of the gastro-intestinal roentgenological examination (Stierlin). There is, in addition to that, hypermotility of the small intestines and colon (Brown,) and frequently iliac stasis. Pirie, and recently Levy and Haft, have confirmed Stierlin's observations, as have most authors.

Carcinoma of the cecum as a rule offers no difficulty in diagnosis, as it usually presents on palpation a hard and palpable mass in the cecal region. Actinomycosis of the cecum can only be diagnosed if the process spreads to the skin, causing the skin to become adherent to the underlying structures, and if actinomycosis can be found in other parts of the body.

A very rare disease of the cecum simulating appendicitis was

recently reported by Cooke.³² The operation disclosed the cecum to be the seat of multiple diverticuli which harbored a concretion. As this concretion increased in size it caused pressure, necrosis and an extensive inflammatory deposit.

Another rare affection simulating chronic appendicitis is tuberculous glands in the ileocecal region, without affection of the cecum or ileum, especially if these glands cause pressure on the ileofemoral nerve. This is much more common in younger individuals than in those of adult life. I have encountered cases where scoliosis of the lumbar region, either congenital or acquired, may give rise to pains in the appendicular region. The acquired form of scoliosis of the lumbar region may be encountered in hip disease or in atrophy of the muscles of the hip and thigh, the results of poliomyelitis. Of course, in these cases, the history, the general physical examination and the roentgenological examination of the lumbar vertebra, will guard against mistake.

Finally, diseases of the right ovary and tube, as well as diseases of the prostate, may simulate chronic appendicitis. Chronic appendicitis may also be simulated by stones in the right kidney and especially in the right ureter. This is especially true in cases where the stone lodges in the kidney or ureter, not passing into the bladder. Here, too, a careful examination of the urine, the positive Murphy sign, tenderness over the right testicle, and above all, the roentgen-ray examination, and, if necessary ureterscopic examination, will aid in establishing the proper diagnosis.

To the second group, diseases resulting from chronic appendicitis, belong functional gastro-intestinal diseases secondary to chronic appendicitis, organic intra-abdominal diseases secondary to chronic appendicitis, extra-abdominal diseases, and other diseases of the appendix.

The functional diseases are hysteria and neuresthenia. It cannot be too strongly emphasized that just as hysteria and neuresthenia may simulate chronic appendicitis, so may chronic appendicitis, by causing persistent suffering, lead to hysteria and neuresthenia in a predisposed individual.

Spasm of the cecum may also be secondary to chronic appendicitis in predisposed individuals. The relation of calcium metabolism to persistent spasmophilia in the adult was clinically pointed out by Perez³³ in Berlin, and was later experimentally demonstrated by Krauss and Zondek. Recently, Kauffmann³⁴ contributed a very interesting article on this subject. If spasmophilic individuals develop any organic disease, the spastic phenomena are so pronounced that the underlying organic disease may be overlooked, or, if such individuals develop a marked organic disease the spastic phenomena may be aggravated and the differential diagnosis is, therefore, sometimes quite impossible.

To the functional gastro-intestinal diseases secondary to appendicitis belong the functional secretory, sensory and motor disturbances

of the stomach and colon. The functional secretory, sensory and motor disturbances in the stomach secondary to chronic appendicitis may be such as to fully simulate gastric or duodenal ulcer. In severe cases they may even cause marked delay in the emptying of the stomach. The differential diagnosis is made possible in most cases by the roentgen-ray examination, which aids in excluding gastric or duodenal ulcer, and shows some or all of the roentgenological signs characteristic of chronic appendicitis named above.

Chronic appendicitis may sometimes cause secretory and motor disturbance in the colon, giving rise to colica mucosa, marked enterospasm, or even severe constipation, or sometimes constipation alternating with diarrhea, and in rare cases, only diarrhea.

The intra-abdominal diseases secondary to chronic appendicitis deserve special mention, as both pathology and clinical studies have taught us that chronic appendicitis may be the cause of ulcer of the stomach (Roessle) or of gall-bladder infection (Moynihan, Mayos, Rolleston), and cause widespread adhesions, giving rise to varying degrees of colonic and iliac stasis. These diseases need no further discussion here as they have been sufficiently discussed above. Of the intra-abdominal diseases giving rise to secondary chronic appendicitis, affections of the female generative organs, especially that of the right tube and ovary are of practical consideration. The differential diagnosis, as a rule, is not difficult, if careful vaginal and rectal examinations are systematically carried out.

It must be emphasized again that the statement of Sahli, that the appendix is the abdominal tonsil, which, if diseased, is productive of a great deal of evil, undoubtedly holds good. This evil effect not only makes itself felt in the intra-abdominal viscera, but may also cause extra-abdominal disease.

Among the extra-abdominal affections may be mentioned chronic joint diseases, some endocrine diseases (thyrotoxicosis and, very rarely, Addison's disease). It may also be mentioned that chronic appendicitis is at times associated with right-sided pleurisy. How this occurs was explained by the experimental studies of Putzianus,³⁵ who demonstrated that an infection of the lymph vessels of the cecum and appendix sometimes results in right-sided pleurisy, whereas infection of the cecal veins never cause pleurisy. This may explain the case quoted above where there were attacks of hoarseness, possibly due to mediastinal pressure on account of lymphatic infection of the mediastinal pleura, the result of chronic appendicitis, and in which the symptoms disappeared after the removal of the appendix.

Some authors have also encountered frontal sinusitis and pansinusitis, the result of a chronically infected appendix.

Other diseases of the appendix which simulate chronic appendicitis are: primary tuberculosis, primary carcinoma and primary actinomycosis of the appendix. These diseases are, in most cases, not diagnosed before operation.

Prognosis. From what has been said above, the prognosis depends on a great many factors. That chronic appendicitis may give rise to an acute exacerbation with all its dangers, is well known. Chronic appendicitis uncomplicated by functional disturbance or by adhesions or by other organic disease of the gastro-intestinal tract gives a good prognosis, if the appendix is removed. If, on the other hand, it is harbored by a neuropathic individual, the outlook depends entirely as to what is primary and what is secondary. If chronic appendicitis is primary, the removal of the appendix will likewise remove the symptoms. If, on the other hand, the neuropathy is primary, the removal of the appendix is of but little benefit. The primary disease must be treated in order to obtain results. If chronic appendicitis is the cause of adhesions, the prognosis depends considerably upon the position of the adhesions, and whether they can be surgically treated or not, and likewise upon the judgment of the surgeon handling the adhesions.

BIBLIOGRAPHY.

1. Oberndorfer: Pathologische Anatomie des Wurmfortsatz, Lubarsch-ostertag Ergebn., 1909.
2. Deaver: Jour. Am. Med. Assn., 1910, 55, 2198.
3. Rotter: Ueber Perityphilitis, Berlin, 1896.
4. Aschoff: Ergebn. d. inn. Med. u. Kinderh., 1912, 9, 1.
5. Rheindorf: Die Wurmfortsatzenzundung, Berlin, 1920.
6. Cecil and Bulkley: AM. JOUR. MED. SCI., 1912, 143, 793.
7. Wilson: Brit. Med. Jour., 1912, 1, 829.
8. Maresch: Wien. klin. Wchnschr., 1921, 34, 181.
9. Moynihan: Brit. Med. Jour., November, 1908, p. 1597.
10. Lichty: Ohio Med. Jour., December, 1915, p. 779.
11. Rolleston: Brit. Med. Jour., 1920, 1, 317.
12. Hurst: Arch. Roentgen-ray, 1914, 29, 249.
13. Mac Kenzie: Symptoms and Their Interpretation, London, 1920, p. 67.
14. Roessle: Das Magengeschwür eine zweite Krankheit, Mittel, Greunzgeb., 1912, 25, 776.
15. Eppinger and Hess: Ztschr. f. klin. Med., 1909, 67, 205, and 68, 345.
16. Chartier: L'encephal, 1913, 8, 44.
17. Fenwick: Lancet, March, 1910, p. 706.
18. Schnitzler: Med. klin., 1913, 38, 1538, and 1913, 39, 1584.
19. Ransohoff: AM. JOUR. MED. SCI., 1923, 165, 202.
20. Quimby: New York Med. Jour., October, 1913, p. 697.
21. Case: Am. Jour. Roentgenol., August, 1914, p. 376.
22. Imboden: Am. Jour. Roentgenol., January, 1915, p. 581.
23. Eisen: New York Med. Jour., August, 1915, p. 352.
24. Cohn: Deutsch med. Wchnschr., March, 1913, p. 606.
25. Hurst: Arch. Roentgen-ray, 1914, 19, 249.
26. Groedel: München. med. Wchnschr., April, 1913, p. 744.
27. Case: Am. Quart. Roentgenol., 1912-13, 4, 77.
28. Spriggs and Marxer: Lancet, 1919, 116, 91.
29. Lieck: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1920, 32, 153.
30. Stierlin: München. med. Wchnschr., 1911, 58, 1231.
31. Brown and Sampson: Jour. Am. Med. Assn., 1919, 63, 77.
32. Cooke: Jour. Am. Med. Assn., February, 1922, p. 578.
33. Perez: Spezielle Pathologie und Therapie innerer Krankheiten, Kraus u. Brugsch; Deutsch med. Wchnschr., 1920, 8, 201; Arch. f. exp. Path. u. Pharmakol., 1920, 87, 342.
34. Kauffmann: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1923, 36, 96.
35. Putzianus: Matthes Differentialdiagnose inner Krankheiten, Berlin, 1923, p. 288.

DISEASE OF THE MEDIASTINUM AND ITS CONTENTS.

BY CHARLES EDWARD HAMILTON, M.D.,

BROOKLYN, N. Y.

UNTIL comparatively recent years there was no region within the body in a more nebulous state, insofar as our diagnostic capabilities were concerned, than that relatively small region within the thorax, the mediastinum. Within this small area are contained many varied structures, each capable of undergoing pathological changes in the early stages with no symptoms whatever being manifested, and only showing evidence of these changes when they are very extensive, shortly before death. Or should symptoms be present early, they are as likely to be produced by pressure on some other structure within the mediastinum as they are by the offending structure itself. Because of its former inaccessibility to diagnostic procedure, it has been held sufficient to designate any condition with a symptom-complex referable to the mediastinum, as mediastinal tumor, without attempting to make a true pathological and anatomical diagnosis. The many advances made in our diagnostic armamentarium in recent years, have made it possible at the present day to diagnose rather concisely the nature of lesions within the mediastinum as well as its anatomical location.

The mediastinum is that space lying between the right and left pleura laterally, and extending from the sternum anteriorly to the vertebral column posteriorly. A line running from the junction of the manubrium and body of the sternum anteriorly to the lower part of the body of the fourth thoracic vertebra posteriorly, divides this area into a superior mediastinum, that space above the line bounded by the manubrium in front and the upper four thoracic vertebræ posteriorly, and a space below the line. This lower area is divided by the pericardium into an anterior mediastinum lying in front of the pericardium, a middle mediastinum containing the pericardium and its contents, and a posterior mediastinum lying behind the pericardium. The middle mediastinum containing the heart is by far the largest of these subdivisions.

The anterior mediastinum is very small because of the reflections of the pleura anteriorly, which go behind the manubrium from the sternoclavicular joints on either side to the middle of the sternum at the junction of the manubrium and body of the sternum; from there to the fourth costal cartilage, both pleural membranes being in contact, and at this point the right layer continuing down to the xiphoid process, while the left layer diverges slightly laterally and continues down to the sixth costal cartilage. Within the mediastinum are contained normally the thymus, trachea, bronchi, esophagus, heart and great vessels, lymph nodes, thoracic duct and

the vagus, phrenic and sympathetic nerves. At times it may also contain an enlarged thyroid or an accessory thyroid.

In order to diagnose conditions arising within the mediastinum, a knowledge of the pathological conditions that can occur within this space must be known. These may be under three headings:

1. Inflammatory.
2. Traumatic.
3. New growths.

Inflammatory processes within the mediastinum and its contents may be either acute or chronic. It is impossible to detect simple acute mediastinitis unless the acute condition is suppurative. This condition is not uncommon, and practically always is secondary to some other disturbance within the body. It may occur through extension from pneumonia or some other inflammatory condition of the lung or pleura, from osteomyelitis of the bony thorax or cervical or thoracic vertebræ, from an inflammatory condition in the deeper structures of the neck, especially a retropharyngeal abscess, from suppuration of the mediastinal lymph nodes or from an ulcerative process within the trachea, bronchi or esophagus. It may occur as a metastatic lesion in the course of a septicemia or erysipelas. It may follow trauma to the thorax with or without perforation of its wall and lodgment of foreign bodies within. Occasionally a case is met with in which no etiological factor can be discovered, and should be considered as a case of primary suppurative mediastinitis.

Generally the pus in this condition is localized or encysted in the anterior, middle or posterior mediastinum or laterally in the mediastinum. Rarely the entire mediastinum is involved in the process. When the pus lies in the anterior mediastinum it is very difficult of detection, as it lies directly beneath the sternum and in front of the cardiac outline, and gives little in the way of signs or roentgen-ray evidence. When involving the middle mediastinum there is, of course, a purulent pericarditis greatly widening the cardiac outline. The pus in the pericardial sac may be either encysted in one part of the sac or generalized. In the posterior mediastinum the condition generally is due to disease of the spine or lodgment of foreign bodies. Laterally in the mediastinum, it is usually subsequent to pneumonia. These abscesses within the mediastinum may rupture into any of the structures contained there, causing fatal hemorrhage or other septic conditions, or they may penetrate through the chest wall.

Chronic mediastinitis is simply a low-grade inflammatory condition without production of pus. It is evidenced by marked distortion and twisting of the structures within the mediastinum, due to extensive fibrous tissue replacement of the tissue normally present. It may result from the acute suppurative condition, but generally results from extension of a pleuropericarditis, tuberculosis,

syphilis or rheumatic conditions. Occasionally it is due to actinomycosis.

Traumatic lesions of the mediastinum occur not infrequently. Foreign bodies, such as bullets, may penetrate the thorax and lodge within the mediastinum, sharp instruments may pierce the chest and enter the mediastinum, or fragments of broken bones may lacerate the mediastinal tissues. Such injuries as these result in abscess formation in a large percentage of the cases, or abscess may result from an injury to the thorax without perforation into the mediastinum. Foreign bodies may lodge within the trachea or its bifurcation, or the esophagus, and cause secondary inflammatory conditions. As a result of trauma there may be found a good sized hematoma within the mediastinum.

A somewhat more serious result of trauma is the occurrence of mediastinal emphysema. This condition arises most commonly secondary to pulmonary disease or whooping-cough. It also occurs following operations at the base of the neck, especially for tuberculous glands or thyroid disease, or following tracheotomy. It may occur, following ulceration of the trachea or esophagus, by processes within these structures.

An unusual cause is artificial pneumothorax. The air may localize within one of the mediastinal spaces, such as within the pericardium or within the anterior mediastinal tissue. It may, however, be more extensive and spread into the superficial tissue of the thorax and into the neck.

The greatest number of pathological processes occurring within the mediastinum, come under the heading of new growths, benign or malignant. Benign growths are quite infrequent in occurrence, and include fibroma, myoma, lipoma, myxoma, chondroma, osteochondroma, simple cysts, dermoids, hydatids, teratoma, neuroma, hematoma and gumma. Of the benign tumors, the dermoid cyst is probably the one most commonly found. As a rule, it occurs in young adults, generally being located about the hilus area or just below, and being either single or multiple. Should it contain teeth or bone tissue, it renders the diagnosis a simple matter. Hydatids when found are generally in association with hydatid disease elsewhere within the body. Lipoma is probably the next most frequent of the simple growths, and these may obtain tremendous proportions. Fibroma may arise from the sternum or cellular tissue of the mediastinum. Chondroma and osteochondroma are rare, and arise from the sternum, costal cartilages or vertebral column. Hematoma may be found of large size. It may result either from trauma or one of the blood diseases, such as purpura. Sometimes it occurs in the course of one of the acute exanthemata. The remaining benign growths, including the gumma, are very rare and not capable of diagnosis, other than as a mediastinal tumor, except at operation or postmortem.

Malignant growths of the mediastinum are of much greater frequency than benign growths. Males predominate over females as to the occurrence of these tumors in the ratio roughly of $2\frac{1}{2}$ to 1. The sarcoma occurs more frequently than does the carcinoma. Sarcoma arise from the connective tissue of the mediastinum, lymph nodes or thymus. Carcinoma arise from the epithelium of the esophagus, trachea, bronchi, thymus or accessory thyroid.

It will probably be easier to consider these malignant growths according to the structure within the mediastinum from which they arise, together with other conditions that may occur within these same structures. Thus, in the glands, in the following conditions enlargements occur:

1. Simple lymphoma, inflammatory, as after measles; typhoid or whooping-cough, tuberculosis, syphilis or in pneumoconiosis.
2. Leukemia, lymphatic, myelogenous or pseudo.
3. Lymphadenoma.
4. Hodgkin's disease.
5. Lymphosarcoma.
6. Metastatic involvement.

The thymus may enlarge, due to simple hypertrophy, cysts, lymphosarcoma or carcinoma. The trachea and bronchi may have papilloma, chondroma or carcinoma. The esophagus may show diverticula, cardiospasm, stricture, either malignant, traumatic or specific, or congenital atresia. It may also show a tracheo-esophageal fistula.

Arising from the nerves we may find neuroma, ganglioneuroma, glioma or neuro-epithelioma. Occasionally there occurs a tumor within the mediastinum, due to enlargement of the thyroid either from simple hypertrophy, cysts, malignant disease or due to an accessory thyroid gland. Large aneurysms, which may be single or multiple, or an aortitis may occur within the aorta. In the heart congenital lesions, such as valvular disease and dextra cordia, hypertrophy of the heart with or without valvular disease, aneurysm of the heart, or tumors of the heart, myxoma, sarcoma or rhabdomyoma, may occur.

Symptomatology. From the standpoint of symptomatology, pathological changes within the mediastinum vary considerably. The usual picture is that of marked dyspnea, cyanosis, puffy face and neck, with distended veins in the neck and over the thorax. A picture such as this represents an underlying far-advanced pathological process. On the other hand, the processes when first occurring, or even when moderately advanced, may present no symptoms whatever to attract attention to this region, and may be detected merely by a casual fluoroscopical examination. However, most of the cases do present definite symptoms for which the patients seek relief, these symptoms mainly being due to mechanical alteration within the structure involved or mechanical affects on structures adjacent to it.

Pain is the most common symptom of which patients complain. The pain in mediastinal disease may vary greatly in its characteristics. It may be constant, dull, boring in type, or intermittent and stabbing, or knife-like in character. Due to pressure on the intercostal nerves, it may be neuralgic in type, radiating along the course of these nerves. It may also occur over the cardiac area and radiate to the neck and down the arm as an anginoid pain. There may be no pain whatever, but simply a sense of oppression or tightness within the thorax.

Disturbances in the respiratory function are very common, the most frequent disturbance being in the form of dyspnea. This, as a rule, is inspiratory in type and may be persistent or periodic, resembling an attack of asthma. It is a most distressing condition to the patient.

Cough is generally present and varies from an occasional dry cough to the most severe types, and may be either persistent or spasmodic. A cough that is fairly typical is the so-called "gander cough." The cough may be associated with varying amounts of expectoration, amounting in some cases to a definite bronchorrhea. Hemoptysis may occur in some cases, and with a dermoid cyst the patient may expectorate hair.

Secondary changes may occur within the larynx, or because of involvement of the laryngeal nerve causing hoarseness or even complete loss of voice. Disturbances in the action of the heart, such as palpitation, irregularity, precordial pain, cyanosis, syncope and edema may be complained of. There may be difficulty in swallowing, a sensation as though food was sticking in the throat, or the vomiting of foul material when the esophagus is involved. Chills and fever, loss of weight, epistaxis, tinnitus, deafness and vertigo may be secondary symptoms. Occasionally the first thing of which the patient complains is a small swelling coming through the thorax.

Physical Examination. On physical examination of the patient, definite signs may be found pointing to a disturbance within the mediastinum, or through complete lack of signs a definite process within this space may be overlooked. The physical findings in mediastinal disease invariably when present point to the diagnosis of a tumor, except for a few conditions in which more distinctive and characteristic findings are noted. Thus, in the acute inflammatory conditions, in addition to the signs of a tumor, a septic type of temperature and an increased leukocyte count may occur. There may be also redness of the skin overlying a mediastinal abscess. However, pus may be present without these distinguishing features. Also, some of the non-inflammatory conditions, notably Hodgkin's disease, may give rise to definite elevation of the temperature, and, of course, the terminal stages of any of these conditions may do the same thing.

In chronic inflammatory conditions a rough creaking to-and-fro friction sound may be elicited under the manubrium when the arms are moved up and down, as in artificial respiration. Also there may be heard in the right second interspace, close to the sternum, a loud blowing murmur independent of the cardiac cycle and increased by holding the breath and deep breathing. This sign I have never been able to detect.

With mediastinal emphysema the signs are generally characteristic. These are hyperresonance or tympany on percussion and on auscultation, a peculiar tinkling sound will be heard under the sternum in systole and diastole. Should the emphysema be more extensive and invade the superficial tissue of the thorax or neck, one may, of course, feel the "egg-shell" crackling on palpation.

Cardiac lesions also have some rather distinctive findings. Foremost among these findings, of course, are heart murmurs. These are valuable, but heart murmurs may be functional, and murmurs may be produced within the heart due to displacement of that organ.

The location of the apex-beat and the palpation of thrills also are important, as are abnormal pulsations over the thorax, irregular pulse and poor heart sounds. Percussion of the cardiac outline, of course, is very important, but it is very difficult sometimes to determine whether one is percussing the border of the heart or a tumor mass spreading out from the mediastinum.

It is surprising what large aneurysms may exist without presenting any physical signs. Of course, there are found characteristic signs, such as tracheal tug, pulsation of sternum, aortic murmurs, bulging of thorax, unequal pulses and diminished breath sounds over one lung from pressure on the main bronchus.

Excluding the conditions mentioned above, the best evidence on physical examination indicative of mediastinal pathology is brought out on percussion. There may be definite symptoms strongly suggestive of a process in this space, but no conclusive signs can be elicited other than marked dulness or flatness, extending out from the median line further than normally warranted either anteriorly or posteriorly over the thorax.

Secondary changes due to the mediastinal process may be noted in other parts of the body. From pressure on the veins one may get suffusion of the conjunctivæ, staring eyes, cyanosis or lividity of the face, edema of the face, neck and extremities, ascites, pleural effusion, dilated veins in neck and over the thorax, localized edema of the thorax. There may be paralysis of the diaphragm from pressure on the phrenic nerve, paralysis of the vocal cords from pressure on the recurrent laryngeal nerve, inequality of the pupils with dilatation or contraction of the pupil on the affected side from pressure on the sympathetics.

When the attention is focussed on the possibility of an abnormal

condition existing within the mediastinum because of any of the symptoms or physical signs enumerated, the history and physical examination alone may be sufficient to warrant definite diagnoses in some of the cases. A history of trauma to the chest, with or without the penetration of foreign bodies, will immediately bring to mind the probability of a mediastinal hematoma, emphysema or lodgment of foreign bodies there, with resultant abscess formation. A history of an inflammatory process in the lungs or bony thorax, with physical signs in the mediastinal area, will suggest the possibility of abscess formation within the mediastinum. Similarly, a history of malignancy somewhere in the body, with physical signs and symptoms implicating the mediastinum, immediately suggests metastatic involvement.

Excluding the few conditions mentioned previously, it is necessary, in the main, for a definite diagnosis of mediastinal conditions, to rely on other measures than the routine physical examination. Many of these conditions that generally have rather typical signs may occur without showing any of these signs. A most important procedure in the diagnosis of mediastinal conditions is to discover whether or not there is any abnormal condition in other parts of the body. Should one find in association with symptoms and signs, indicating a process within the mediastinum, enlargement of lymph nodes elsewhere in the body, palpable liver or spleen or other abdominal masses, and inflammatory processes within the body, it would help considerably in diagnosing the nature of the mediastinal condition in all probability.

Roentgen-ray Examination. In attempting to locate the structure within the mediastinum involved in the pathological process, the roentgen-ray examination is invaluable, and a few general remarks concerning its application will not be amiss. First of all, while the roentgen-ray may give a shadow indicating a definite abnormal condition present, yet that shadow might not possess sufficient characteristics to enable us to state the tissue from which it arises.

Of course fluoroscopy should always be employed in conjunction with the plate examination, fluoroscopy, if anything, being the more important method to use, as one can view the mediastinum by this method in the various oblique positions, and also can see pulsations if any are present. It is very important to determine whether or not the mediastinal shadow pulsates, as this is generally the distinguishing sign of an aneurysm; but an aneurysm may not pulsate, due to an organized clot being contained within it, while many tumors lying adjacent to the heart and aorta may pulsate, due to transmission of the impulse from the heart. If the aorta is suspected of being the cause of the shadow, and yet the shadow does not pulsate, turn the patient in the oblique positions and trace the aorta throughout its course within the thorax to determine whether or not it is abnormal.

Should a mediastinal shadow be seen on fluoroscopy, before drawing a conclusion as to its location and character, the esophagus should be viewed by means of an esophageal paste. By this method, many pathological conditions will be proven to be occurring within



FIG. 1.—Large saccular aneurysm of the ascending portion of the aorta. Shadow showed no pulsation whatever. Because of this fact and its large size and sharply defined borders, case was considered probably a lymphosarcoma. At autopsy a large organized clot about the size of a large grapefruit was found within the aneurysmal sac.



FIG. 2.—Dermoid cyst of mediastinum. Note its triangular appearance due to pressure. Shadow showed a marked transmitted pulsation due to its nearness to heart. Clinically considered a pulsating empyema.

the esophagus, and also many conditions considered to be abnormalities of the esophagus will be seen to be conditions outside of the esophagus pressing on its walls. This method will reveal the

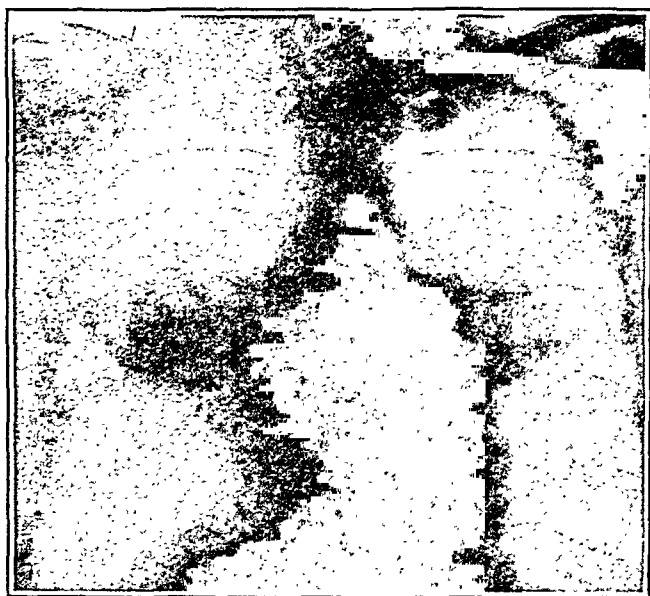


FIG. 3.—Case of pneumoconiosis in a miner, showing marked bilateral involvement of the mediastinal glands.



FIG. 4.—Hodgkin's disease of mediastinum, with involvement of the glands mainly on the right side.

diverticula filling-up and then overflowing into the esophagus, the cardiospasm with its marked dilatation of the esophagus, the tracheo-esophageal fistula or esophageal stenosis, or the stricture of the esophagus malignant, syphilitic or traumatic.

Lesions involving the mediastinal glands usually appear as a bilateral mass at either hilus area. Some cases of glandular involvement may, however, be unilateral. A somewhat characteristic



FIG. 5.—Case of substernal thyroid. Note the shadow extending down from the neck sharply defined with its base in the neck.

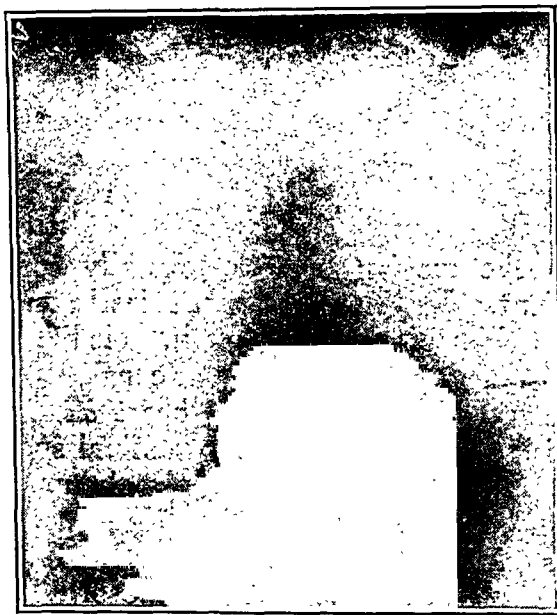


FIG. 6.—Case of encysted mediastinal abscess following pneumonia. Abscess overlying the heart shadow on the left side. Note its sharply defined convex outer margin.

appearance of glandular masses is that the outer border is scalloped in its outline. Of course the etiology of the glandular involvement is not revealed by the roentgen-ray.

Thyroid enlargements generally appear as a shadow extending down from the neck with its lower border convex downward.

These tumors may also be seen to move with the act of swallowing. Thymic enlargements extend much lower down in the mediastinum than do those of the thyroid and sometimes are of such a large size as to cover a considerable portion of the heart outline. When smaller they are generally seen as a shadow extending out on the right side only.

Of the cardiac conditions, dextracardia and cardiac hypertrophy, many times quite typical of a certain type of valvular disease, are easily recognized. Pericardial effusion may show as an enlargement of the total heart shadow or, if the effusion is encysted, simply as a localized enlargement of the heart area not conforming to any known type of hypertrophy. No definite cardiac pulsation can be detected in the outline of this shadow, and also its outlines may be changed by a change in posture of the patient.

The benign growths are generally unilateral and have no special characteristics except for the chondroma and osteochondroma, which are very dense in structure. The cysts may be very symmetrically rounded in outline but, as a rule, they are not, because of being subjected to pressure effects. They are, however, very sharply defined in outline, and in the case of dermoids may contain teeth or bony structure.

Air within the mediastinum is, of course, quite typical, showing on the plate as a black shadow with no markings of any sort running through it. Foreign bodies also are quite easy of detection if opaque. Occasionally the foreign body is a non-opaque material lodged at the bifurcation of the trachea. This may sometimes be suspected because of an increased aëration of the lung on the affected side.

Fluid within the mediastinum is generally encysted and also generally purulent. In the anterior mediastinum the amount of fluid present may be too small to be seen, as it lies directly in front of the heart shadow which hides it, or if considerable in amount it may bulge out on either side of the heart shadow and become confused with it. In the posterior mediastinal space, or laterally, the shadow of the fluid always is sharply circumscribed, and has one border at least, convex in outline.

The shadows of fluid in the mediastinum at times may very easily be mistaken for tumors. It may be of advantage, should this be the case, to roentgen-ray the patient at different intervals of time, watching the growth of the shadow and any invasive qualities it may possess, in order to diagnose the condition. There remain some of the benign tumors, tumors of the trachea and bronchi and tumors of the nerves, that may all cast shadows on the roentgen-ray plate but do not possess sufficient characteristics to enable one to definitely diagnose their nature.

Bronchoscopy and Esophagoscopy. Further investigations include bronchoscopy and esophagoscopy. With tumors of the bronchus,

even though they are large enough to cast a shadow on the roentgen-ray, bronchoscopy is the only method of definitely proving that the tumor involves the bronchus and not some other structure.

Laboratory Examinations. Other laboratory measures may still be indicated in order to make our diagnosis complete. Thus, in the case of glandular enlargements a blood count may prove a leukemic disease to be present. A blood count may also be of some value in differentiating an abscess from a tumor. An eosinophilia may indicate hydatid disease or make one suspect actinomycosis. A tuberculin test or sputum examination may reveal the glandular condition to be due to tuberculosis. Finally, if there be any superficial glands one may be removed and sectioned for diagnosis. A Wassermann test may occasionally clear up the diagnosis in an unusual case of aneurysm or enlargement of the glands or in the case of a gumma of the mediastinum.

Summary. With detailed and careful examination and knowledge of the procedure involved, a definite diagnosis of practically all mediastinal conditions can be made, with the exception of some of the benign tumors and tumors involving the nerves. Experience, of course, will teach many short cuts to follow in quickly arriving at a diagnosis of the conditions present in this region, without having to perform all of these tests outlined in each individual case.

REVIEWS.

NON-SURGICAL DRAINAGE OF THE GALL TRACT. By B. B. VINCENT LYON, A.B., M.D., Chief of Clinic, Gastro-intestinal Department of the Jefferson Hospital; Attending Physician (formerly Pathologist) to the Methodist Episcopal Hospital. Pp. 640; 175 illustrations and 10 colored plates. Philadelphia and New York: Lea & Febiger, 1923.

IN September, 1919, the author of this new volume had his first paper published, on biliary tract drainage by means of the capillary duodenal tube. Since this date a literature has been developed on the method which is not entirely in accord with the claims made in this original contribution nor with the somewhat modified contentions made in subsequent articles. The method seemed on first thought a most rational one to cope with the difficult problems of gall-bladder diagnosis and therapy but in application by other workers many facts have been developed which seem to somewhat minimize its value. It is therefore of great interest at this time to receive a book from the author's pen; for whatever one may believe about the possibilities of non-surgical drainage of the gall tract, its author deserves much credit for suggesting a diagnostic and therapeutic scheme having potential possibilities. He has put much energy into his work and has shown a genuinely honest enthusiasm.

The book contains thirty-six chapters. Ten of these chapters are devoted to the presentation of fifty case reports, somewhat in protocol style with added discussion and comment. Twelve of these case reports were not under the author's care. Other chapters take up the embryology, histology, anatomy, physiology and chemistry of the hepatic tree. Still others are devoted to various aspects of gastro-intestinal diagnosis, gastric analysis, stool examination, functional liver tests and, of course, one chapter to an abbreviated description of the technic of non-surgical drainage of the gall tract and still another to a more detailed description of the technic. A very good chapter on enzyme activity in the duodenum is contributed by Olaf Bergeim. Kolmer has written part of a chapter on bacteriological technic, Manges has written a chapter on roentgen-ray diagnosis of gall-bladder disease and Cheney one on the clinical differential diagnosis of the same disease. Besides the engraved illustrations and colored

plates, very elaborate forms of various types have been included. These are used by the author in his case records. Adverse criticism of the claims made for biliary drainage, as developed in the volume and previously in the author's articles, would make a large paper in itself. It is sufficient, however, to say that the current literature will supply this for those who may be interested. It may be said fairly that the author has called attention to some exceedingly important points in connection with biliary tract disease. He has started what, we believe, will be very fruitful work in this field. Gall-bladder disease is a most difficult subject and is upon uncertain ground. Conclusions on diagnostic aids and efficacious therapy must be cautiously made. Any methods, however, that offer hope are acceptable. S.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Member of the Committee on Nomenclature and Classification of Diseases of the American Medical Association. Twelfth edition. Pp. 1296. Philadelphia: W. B. Saunders Company, 1923.

For nearly twenty-five years this dictionary has been one of the model dictionaries published in America. It is in all respects an extremely valuable work, as the number of editions and length of time that it has existed shows. In the present new edition the volume has been increased in size by 99 pages by the addition of nearly three thousand new words. The physician who has need of a dictionary, and most physicians do need a new dictionary every few years on account of the large number of new words that are coming into medical terminology, may rest assured that if they purchase Dorland they are securing a volume which is a standard and thoroughly satisfactory from their standpoint. M.

FOOD FOR THE DIABETIC. By MARY PASCOE HUDDLESON, Consulting Dietitian. Pp. 75; 2 illustrations. New York: The Macmillan Company, 1923.

Food for the Diabetic was written for the patient, to be used by him as a guide to the control of the diet as well as to indicate to him methods of preparation of attractive diabetic food. This small volume will be of great assistance to the physician if it is placed in the hands of his diabetic patients. It not only deals with diet, but also gives very sensible directions as to the general care of the diabetic patient himself. M.

LEHRBUCH DER GRENZGEBIETE DER MEDIZIN UND ZAHNHEILKUNDE. Edited by DR. JULIUS MISCH, Berlin, in collaboration with numerous authorities. Third edition. Two volumes. Pp. 1382; 596 illustrations, many in colors. Leipzig: F. C. W. Vogel, 1923.

THE fact that the third edition of this work has appeared within a few months after the second is sufficient evidence of its popularity in Germany. In it is presented all of the information about diseases of the body as a whole deemed necessary in the education of the dentist as a mouth specialist, and, on the other hand, the internist as well as specialists in various fields will find here a very complete description of the mouth symptoms of different general diseases. The subject is dealt with in turn from the standpoint of the internist, the pediatricist, the neurologist, the syphilographer, the dermatologist, the gynecologist, the otolaryngologist, the ophthalmologist, and the specialist in industrial diseases. With this arrangement a good deal of repetition is necessarily unavoidable, adding considerably to the bulk of the volumes. It is evident that less importance is ascribed in Germany to oral foci of infection as causative factors in arthritis and other conditions than in America. Perhaps the most commendable section is that concerning the manifestations of industrial diseases in the mouth. To obtain the information here collected in one volume one would ordinarily have to search an entire library. The illustrations, many of them in colors, could hardly be excelled. It is a matter for regret that there is no such work as this in the English language. I.

GRUNDRISS DER INNEREN MEDIZIN. By DR. A. VON DOMARUS, Director of the Medical Division of Auguste Victoria Hospital, Berlin-Weissensee. Pp. 640; 58 illustrations. Berlin: Julius Springer, 1923.

CALLED an "Outline" this book is virtually a text-book on medicine, covering the field almost as fully as the standard one-volume English works. The subject matter is well presented and with few exceptions (*e. g.*, insulin in diabetes, sensitization in asthma, electrocardiography) is adequate and up to date. The reviewer was particularly impressed by the physical characteristics of the book. A handy, simply-bound medium octavo of 640 pages with compact but clear and pleasing print, the volume is just an inch thick and weighs 2.5 pounds (in contrast to the one-volume English texts that average over 4 pounds). A similar make-up might be recommended to American publishers: a text-book could be sold for half the present rates—smaller initial profit, but far more likely to "repeat" in new editions. K.

APPLIED PSYCHOLOGY FOR NURSES. By DONALD A. LAIRD, Assistant Professor of Psychology, University of Wyoming. Pp. 236; 49 illustrations. Philadelphia: J. B. Lippincott Co., 1923.

THE selection of subjects which the book presents is admirably suited to the work of nursing. The arrangement is very good indeed but the amount of material given under the themes is wholly inadequate to teach them successfully to girls who are entering into the field of nursing. A book covering as many subjects as these must be considerably extended in order that the subjects will be taught; as it is, the book is neither a dictionary nor a text. It should be either one or the other. B.

DIATHERMY AND ITS APPLICATION TO PNEUMONIA. By HARRY EATON STEWART, M.D., Attending Specialist in Physiotherapy, U. S. Marine Hospitals, N. Y., Director, New Haven School of Physiotherapy. Pp. 210; 45 illustrations. New York, Paul B. Hoeber, 1923.

THIS volume is a short description of diathermy technic together with an account of its application in the treatment of pneumonia. The author is enthusiastic about this treatment, but of course it is impossible to draw conclusions from 67 cases of a disease such as pneumonia which varies so in severity of symptoms in different individuals and in the virulency of the disease at various times.

M.

CLINICAL LABORATORY DIAGNOSIS. By ROGER SYLVESTER MORRIS, A.B., M.D., Professor of Medicine in the University of Cincinnati and Director of the Medical Clinic of the Cincinnati General Hospital. Pp. 456; 99 illustrations. New York, D. Appleton & Co., 1923.

A BOOK on clinical laboratory methods and diagnosis which is designed for the use of students and practitioners of medicine as is this book should fulfil several requisites. It should be convenient in size; the directions should be clear and terse; the methods of performing the various tests should be those that have been proven by actual use to be practical and valuable; it should be written by one who is experienced in the actual manipulations and performances of the tests, and, lastly, in order to correlate the laboratory diagnosis with the clinical it should contain a certain amount of clinical data. All these requisites are found in this new volume by Dr. Morris. In addition to the clear-cut presentation of the subject it might be

added there are several features that are particularly of value. In the first place the references are well given and there is also an index to the authors as well as an index of subjects. There is a splendid table on normal and pathological blood chemical analyses. Pathological blood conditions are classified, for example; twenty-three causes of lymphocytosis, seventeen causes of mononucleosis and so on. And lastly the illustrations are well selected, while those of the blood are particularly good, the author being the artist. Dr. Morris is to be congratulated upon his work. The reviewer feels confident that he can predict for it a long life and great popularity.

M.

INTERNATIONAL CLINICS. Volume IV, 33d Series, 1923. Pp. 308. Philadelphia: J. B. Lippincott Company, 1923.

DR. THAYER has a most interesting contribution in the present number of *International Clinics*. There is also a splendid symposium on gastrointestinal ulcers, a most interesting review on otology for the medical student by Dr. Randall as well as the Alvarenza Prize essay of the College of Physicians of Philadelphia for the year 1923 on Echinococcus Disease. In addition to these outstanding contributions there are more than a dozen other articles on surgery, pediatrics, diagnosis, etc.

M.

THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY IN THE WORLD WAR. VOLUME V. MILITARY HOSPITALS IN THE UNITED STATES. Pp. 857; 204 illustrations. Washington: Government Printing Office, 1923.

THE fifth volume of the governmental history of the Medical Department in the World War is a large volume upon the various types of hospitals, such as were built in this country to supply cantonments, embarkation camps, ports of debarkation, etc. Every type of hospital and every hospital that was constructed or provided for in this country is given more or less detailed mention in the book with particular reference to the base hospitals at the various camps. For each of these hospitals statistics are given concerning the number of sick and wounded that were in the hospital during the various months they functioned and the personnel on duty, as well as a one-to four- or five-page description of the general plan of the hospital. The book is teeming with interesting data; of particular interest from the medical viewpoint is to review statistically the frightful toll that influenza took among the soldiers of this country. For

example, at the Base Hospital at Camp Sherman, Chillicothe, Ohio, commanded by Lt.-Col. Kinard in the month of October, 1918, there were 1056 deaths, the month preceding that there were 28 and the succeeding month 31 which was about the average monthly death-rate in the hospital. The same figures held in about the same proportions in many of the camps throughout the country. This fifth volume is as well presented as the first volume, intervening volumes have not as yet appeared. M.

NEUROLOGIC DIAGNOSIS. By LOYAL E. DAVIS, M.D., Associate Professor of Surgery, Northwestern University Medical School; Fellow of the National Research Council. Pp. 173; 49 illustrations. Philadelphia and London: W. B. Saunders Company, 1923.

THIS short work is an effort to correlate the basic principles of anatomy, physiology and pathology of the central nervous system with the clinical manifestations of disease. The first 62 pages are devoted to a brief consideration of the first mentioned factors, while the remaining 100 pages are devoted to a discussion of illustrative cases, which are well presented, easy to read and in every way extremely instructive. The book should prove of very definite value to the student and internist. M.

FIGHTING FOES TOO SMALL TO SEE. By JOSEPH MCFARLAND, M.D., Sc.D., Professor of Pathology in the Medical Department of the University of Pennsylvania. Pp. 309; 64 illustrations. Philadelphia: F. A. Davis Company, 1924.

"THE war gave us a new word—'Preparedness,'" says the author of this work in his introduction. "Many have insisted that preparedness implies a state likely to be dangerous through the temptation to aggression. In the preparedness against epidemic disease the only aggression is against inhuman foes, from whom we can want nothing, and can take nothing, but by whom we may be invaded, devastated and depopulated. We must fight these foes too small to see." While the book deals with subjects unfamiliar to the average reader, it is written in a way admirably calculated to make him familiar with things of the highest importance to his life and health. The text, which had its beginning in four lectures delivered at the Wagner Free Institute of Science of Philadelphia, is divided into seven chapters, dealing, respectively, with the

Origin of Microorganisms, the historic error concerning the Spontaneous Generation of Life, Effects of Microorganisms, Infection, Transmission of Causes of Disease from Individual to Individual, Prevention of Disease through Increase of Resisting Power and Prevention of Diseases Transmitted by Insects. Sixty-four engravings enhance the popular appeal of the work and its beneficent purpose in dissipating the all too prevalent ignorance of the causes and modes of transmission of diseases, and in combating that apathy and prejudice against new measures which are the chief obstacles to the extinction of infectious diseases.

Especially valuable from the every-day point of view is the author's treatment of such themes as dangers in milk and water; infection from vegetables; efficient and inefficient vaccination; preventing diphtheria; ticks, lice and bedbugs. Much of the concluding portions of the book is devoted to interesting summaries and selections from historic accounts of the plague, or black death, from Gould and Pyle's *Anomalies and Curiosities of Medicine*, Pepys' and Evelyn's *Diaries*, and Boccaccio's account of this malady. There are also detailed descriptions of the latest discoveries in regard to the origin and treatment and prevention of the African sleeping sickness.

W.

HOW OUR BODIES ARE MADE. By R. M. WILSON, M.B., CH.B. Pp. 246; 118 illustrations. London: Henry Frowde, Hodder & Stoughton, 1923.

THIS is an extremely practical and most interesting explanation of physiology for young people and could be very readily used for instruction in elementary schools.

M.

PROBLEMS in TUBERCULOSIS. By SIR JAMES KINGSTON FOWLER, K.C.V.O., C.M.G., M.A., M.D., D.Sc. (HON.), F.R.C.P., Consulting Physician and Emeritus Lecturer on Medicine, The Middlesex Hospital; Consulting Physician to the Brompton Hospital for Consumption and Diseases of the Chest and to King Edward VII Sanatorium. Pp. 64; 1 illustration. London: Oxford Medical Publications, 1924.

THE author has written down here the results of many years of close study of tuberculosis. He presents his impressions in the interesting and rather chatty way which is so attractive in the average English text-book. The book will well repay reading by the internist.

M.

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-
GEON TO THE PHILADELPHIA GENERAL AND
NORTHEASTERN HOSPITALS.

Roentgenological Diagnosis of Cholecystic Disease.—CARMAN, MAC-CARTY and CAMP (*Jour. Radiol.*, 1924, 2, 80) say that it has been impossible to differentiate the roentgen-ray densities of normal and abnormal bile. There is no apparent reason why the normal gall-bladder should not cast a shadow as often as the diseased organ. Various observers have described certain indirect signs of disease of the gall-bladder consisting of deformities of the antrum of the stomach, duodenal cap and second portion of the duodenum supposedly produced by a distended gall-bladder, and certain spastic phenomena, pylorospasm, delayed motility and cardiac regurgitation. Leonard asserted that direct signs are present in but one-third of the cases and that two-thirds of his diagnoses are based solely on indirect signs. In a large series of 343 cases positive report of disease was made in 52.9 per cent and negative diagnosis in 44.6 per cent, when there was evidence of mild or extreme grades of disease. The study of these cases raises the question whether the results warrant the time and expense required for roentgenological examination. All the gall-bladders removed at operation were examined by the pathologist and found to be diseased. The accuracy of roentgenological examination is therefore limited to 50 per cent.

Studies of the Exophthalmic Goiter and the Involuntary Nervous System.—HYMAN and KESSEL (*Arch. Surg.*, 1924, 8, 149) remark that the present study was upon the course of the subjective and objective manifestations in 50 unselected patients observed over a period of two years, in whom no specific measures were instituted. It was noted that in the vast majority of the patients with exophthalmic goiter there was a marked and progressively increasing tendency toward "spontaneous" recovery. Recovery was not complete in the sense

of cure, but was marked by the persistence of residual subjective symptoms. In at least the first two years of the remissions the occurrence of severe incapacitating exacerbations were infrequent. These results of "skilful neglect" compare favorably with the results of specific therapeutic measures.

The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter.—SEGALL and MEANS (*Arch. Surg.*, 1924, 8, 176) say that the early effects of operations amounting to subtotal thyroidectomy in patients with toxic goiter are a rise in basal metabolism and pulse, which can be largely explained on the basis of fever and emotion. A progressive fall in metabolism and pulse brings them within normal limits in from four to twelve days. The rate of detoxication following subtotal thyroidectomy is quite similar to that during the period of recovery from hyperthyroidism induced by thyroid feeding. While pulse and basal metabolism show considerable parallelism, the latter fluctuates less and is the better index of the degree of hyperthyroidism.

The Clinical Diagnosis of Carcinoma of the Breast.—BATTLE (*Lancet*, 1924, 1, 206) states that the swellings which it may be difficult to distinguish from early carcinoma of the breast are cysts, fibroadenomata and chronic inflammation. When the cysts and fibroadenomata are associated with local inflammation the diagnosis becomes at times impossible. Sometimes a simple cyst bursts through overstretched skin and a fungating sore develops. It is advisable to explore small swellings (especially after the age of thirty years) about which there is doubt. Exploration should show even in small malignant ones, a cartilaginous resistance to the knife, a hard edge, a cupping of the surface on which there is the appearance of the unripe pear. This picture should not be confounded with anything else. A mistake between tuberculous deposit and carcinoma is not usual in the first stage. The local enlargement is insidious and little may be noticed to cause alarm until suppuration ensues. Some sarcomata develop cartilaginous change and so resemble hypertrophic carcinoma in their unusual hardness, but they are usually of more rapid growth. Characteristic invasion of surrounding parts is absent and the hardness is mostly distributed in an irregular manner.

The Selection of Patients and of Operation in the Surgical Treatment of Pulmonary Tuberculosis.—LILIENTHAL (*Am. Jour. Surg.*, 1924, 34, 1 and 2) says that surgery is not intended to supplant medicine in the treatment of tuberculosis of the lungs. It should be resorted to when medical and hygienic treatment have nothing more to offer and the patient's life is intolerable or the prognosis is grave. Operation may have two distinct objects—placing at rest the entire lung and secondly the obliteration of apical cavities. Collapsing thoracoplasty with phrenic nerve resection puts the lung at rest to a greater degree than is possible by any other known method. It is only to be applied when the other lung can function sufficiently to support life and when it is not affected by rapidly developing tuberculosis. Thoracoplasty does not take the place of therapeutic pneumothorax for no return of function is possible. In pneumothorax lung function can

be restored, when desirable, in a large number of cases. Arrest or great improvement following collapsing thoracoplasty may be expected in about 75 per cent of the cases. The obliteration of apical cavities can be performed on both sides of the chest and is worth performing when the disease in the remaining parts of one or both lungs is capable of arrest.

Prognosis in Giant-cell Sarcoma of Long Bones.—COLEY (*Ann. Surg.*, 1924, 79, 321) says that various names have been given this tumor, beginning with tumor *a* myeloplaxes, myeloid sarcoma, giant-cell sarcoma, benign giant-cell sarcoma of the epulis type, giant-cell tumor of Bloodgood, osteitis fibrosa cystica (von Recklinghausen), hemorrhagic osteomyelitis (Barrie). The author's series of 50 cases shows that the disease had existed less than six months in 50 per cent of the cases and more than a year in only 6 cases. The upper end of tibia, lower end of radius and lower end of femur are the most frequent sites. The lower jaw is the most frequent site of other bones. The growth gradually expands the bone, destroying the bone slowly by absorption, but rarely breaking through the periosteum, and still more rarely invading a neighboring joint. The author believes a certain number of these tumors are definitely malignant and cause death by metastases, and that it is not always possible to differentiate the benign from the malignant, especially in the early stages of the disease. There is no uniform method of treatment in giant-cell sarcoma. Immediate amputation is seldom done at present. Curetting with the application of carbolic acid is probably more largely used than any other method. Ewing would give up curettage entirely and substitute routine treatment with roentgen-ray and radium.

Paget's Disease of the Female Nipple.—BLOODGOOD (*Arch. Surg.*, 1924, 8, 461) states that the evidence would suggest that ultimately cancer develops in every ulcer of the nipple. The moment cancer develops in the ulcer of the nipple there may be infiltration of the cancer cells along the ducts. In 13 cases of early cancer of the nipple in only 2 were the ducts free from any evidence of cancer. In only 4 of this series was the author able to demonstrate nests of cancer in the lymphatics of the breast. This is evidence of the danger of any unhealed lesion of the nipple and also clearly demonstrates that there is but one operation for cancer of the nipple, no matter how early, and that is complete operation. The age of the patients with cancer of the nipple has varied from thirty-eight to eighty-four years. The larger number of patients were past the menopause. So far none have been in colored women. The author's whole evidence is against excision of only the breast. It is unnecessary when the lesion is benign, and not sufficient when the lesion is malignant. When Paget's disease is seen in its latest stages it is apparently hopeless from the standpoint of any treatments.

Diseases of the Colon.—CARMAN and FINEMAN (*Jour. Radiol.*, 1924, 1, 129) say that the barium enema has been found of greater value than the ingested meal in the diagnosis of diverticulitis, neoplasms, tuberculosis and chronic ulcerative colitis. Antispasmodics in physio-

logical doses are made use of in cases in which spasticity is present. A non-retention of the barium in the ceco-colon shortly after its filling with the bariumized mixture has been observed in carcinoma, tuberculous and chronic ulcerative colitis. Frequently lesions cannot be detected unless deep palpation and approximation of the bowel walls is resorted to during fluoroscopical examination. Motility has been found of very limited value in the diagnosis of colonic disease. Very small lesions, the extent of the lesion and lesions in the distal half of the colon can usually be best demonstrated with the barium enema. Roentgenological diagnoses of diseases of the colon should, as a rule, be limited to actual shadow phenomena observed—a final diagnosis must be based on a correlation of all known data. A specific diagnosis cannot be made with assurance until a biological examination of tissue removed at operation has been made.

A New Mercurial for the Intravenous Treatment of Syphilis.—SNODGRASS (*Lancet*, 1924, 206, 117) states that this mercurial has been given the name of "flumerin," containing 33 per cent of mercury in the non-ionized form. Gross secondary lesions show material alteration in the direction of healing within one week as a result of the administration of flumerin alone. No other mercurial preparation would appear to produce marked changes so rapidly. The action is not lasting, however. Relapses in secondary cases may occur within a relatively short time or even while treatment by flumerin is being continued. A positive Wassermann reaction is usually not altered to a negative one. In this respect flumerin does not compare unfavorably with an equivalent use of other mercurials given without arsphenamin preparations. Tertiary cases which present definite lesions show rapid clinical improvement with flumerin alone. The rapidity appears much greater than that produced by other mercurials, but less than by the combined treatment by mercury and iodides. Extended trial of flumerin should be made on account of its rapid antisiphilic effect. This rapidity is its outstanding property.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,
OF PHILADELPHIA.

Meningeal Hemorrhages in the Newborn and Their Remote Consequences.—GORDON (*Am. Jour. Dis. Child.*, 1924, 27, 303) says that the cause of meningeal hemorrhage is principally the tearing of the membranes due to their overstretching, which leads to the rupture of the bloodvessels. To produce a tear there must be great cranial stress. Since the latter is often the result of protracted, difficult labor, with instrumental delivery, the obstetrician should bear in mind that

the force used in the application of the forceps should not be excessive, or should not be applied in the wrong diameter of the head, as, for example, the antero-posterior diameter. In the latter case the vertical elongation of the head is more liable than anything else to cause overstretching and tearing of the meninges. Forceps are useful and in many instances have been responsible for the saving of lives, but they may also be responsible for injuries in the fetus leading to consequences that have a direct bearing on the later physical and mental development of the child. With a certain degree of possible errors, supratentorial hemorrhages present a somewhat different clinical picture from the infratentorial type. In the former the blood spreads over the hemispheres of the cerebrum; in the latter over the hemispheres of the cerebellum but also into the medulla. In the former the blood cannot go beyond the lower surface of the tentorium; in the latter the blood reaches the subarachnoid spaces, and may extend into the spinal canal. For these reasons in the supratentorial hemorrhages at birth there is found a bulging fontanelle and a group of nervous phenomena, such as sleeplessness and great restlessness and convulsive seizures with a continuation of the condition. In infratentorial hemorrhage there is considerable depression, apathy, somnolence, early cyanosis, vasomotor and respiratory manifestations and rigidity of the neck muscles. In view of the anatomical differences, respiratory and other bulbar disturbances will not be observed in the supratentorial cases. For anatomical reasons in infratentorial cases lumbar puncture may be of considerable benefit. In the supratentorial cases lumbar puncture does not avail much as the blood cannot reach the subarachnoid easily. Surgical therapy is almost the only issue. Early craniotomy is definitely indicated. Favorable results can only be expected when the operation is performed within a few days of birth. After the clot has already produced damage to the cortical tissue no relief can be expected. It seems logical that in all cases indicating increased intracranial pressure at birth lumbar puncture should be resorted to at once, before a definite localization is made, since in the infratentorial group it is of definite therapeutical value and in the supratentorial the diagnosis may be promptly established.

Convalescent Whole Blood Plasma and Serum in Prophylaxis of Measles.—ZINGHER (*Jour. Am. Med. Assn.*, 1924, 82, 1180) found that convalescent measles serum, plasma or whole blood, had definite value in the prophylaxis of measles. It can be used to produce complete passive immunity if injected within the first four or five days after exposure, and a mixed form of immunity if injected in larger dose after the fifth day. It can be injected in small doses after the fifth day of exposure to modify the character of the disease, rather than to prevent its development. If such an attack develops the immunity will probably be permanent. The blood plasma or serum of recovered cases, such as that from brothers and sisters, and also of adults that have had measles in childhood, can replace convalescent serum if used in large amounts. With the increasing number of days since exposure larger doses of convalescent doses have to be used when it is desired to produce complete immunity. The dose of serum during the first days of exposure is 2.5 cc; during the fifth and sixth days 5 cc, and during

the seventh to eighth days 7.5 cc. To influence the type of measles so that a modified type of the disease will develop, the dose is from 2.5 to 3 cc from the fifth to the tenth day after exposure. These doses are calculated for children three years of age. They should be proportionately higher for older children and adults. A quick, convenient and simple way, which can be used with ease both in hospital and in private practice when prepared convalescent serum is not available, is to inject intramuscularly whole blood, citrated or non-citrated, in double the amounts recommended for the serum. Complete passive protection with convalescent serum or plasma has its field of usefulness in protecting the very young and feeble children and those suffering from rickets, tuberculosis, diphtheria and whooping-cough. Also during the cold seasons of the year, when catarrhal conditions prevail and there is danger of pulmonary complications, such extreme immunization is often indicated. In private practice in dealing with normal healthy children who have been exposed to measles, as well as in some institutions taking care of healthy robust children, it will be generally more desirable to use convalescent serum, the serum of recovered cases or adult serum, so as to obtain a modified and mild form of the disease. A fairly permanent immunity will thus be established, rather than a temporary protection for a short time. In certain institutions, founding asylums and hospitals the indications are to stamp out the outbreak of measles, completely protecting the exposed and non-immune children with convalescent serum. Outbreaks of measles cause a high mortality among these children and cripple the institution badly. The history of previous attacks of measles should carefully be inquired into and recorded for each child admitted to the hospital or institution. Such records will greatly simplify subsequent immunization work with convalescent serum. A supply of convalescent serum or plasma can be obtained and kept on hand if coördinated efforts are made between physician and health authorities. The supply is bound to remain limited. The great value of recovered serum or of adult serum consists of the ability to obtain it from parents or other relatives. Of 102 non-immune children injected after exposure to measles for varying lengths of time, 92 were completely immunized, 7 developed modified measles and 2 developed typical measles. Of these 2 only 1 child was injected before the fifth day of exposure. One child was protected for twenty-eight days, but developed measles after a second exposure. Of 58 additional children injected in two institutions 23 developed mild measles and 4 developed typical measles. These 4 children were injected with 3 cc of a thirty-five-day convalescent plasma. A large dose of this or a smaller dose of a more recent convalescent would most probably have prevented the development of typical cases. Of 37 control children who were not injected 7 developed typical measles and only 3 a mild form.

Studies on the Acidity (Hydrogen-ion Concentration) of Infants' Stools.—TISDALL and BROWN (*Am. Jour. Dis. Child.*, 1924, 27, 312) describe in this paper a simple procedure for determining the hydrogen-ion concentration of infants' stools. In this investigation 1300 determinations were made. The hydrogen-ion concentration from normal newly born babies fed from the mothers' breasts was found to be

singularly constant, varying from 4.7 to 5.1. The acidity of stools from artificially fed infants was found to vary from pH 4.6 to somewhat more alkaline than pH 8.3. An acidity as great as pH 4.6 was encountered in artificially fed infants only in severe diarrheal conditions. Infants fed on butter-soup, cows' milk dilutions with added carbohydrates, and whole soured milk with added carbohydrates, generally had stools more alkaline than pH 7. Whole soured milk with added carbohydrates up to a total content of 20 per cent generally produced strongly alkaline stools. No difference was consistently noted in the acidity of the stool, whether the added carbohydrate was in the form of corn syrup, dextrimaltose or cane sugar. The effect produced by other sugars was not determined. The degree of acidity of the stools was generally increased by the presence of parenteral infections. Based on this work and the work of others, the factors which influence the acidity of the stools have been considered. From the chemical standpoint the acidity apparently depends on the ratio, in the intestinal zone of fermentation, of the carbohydrate on the one hand to the protein and base on the other. The amount of carbohydrate in the zone of fermentation apparently is influenced by the extent of the zone of fermentation, by the type of carbohydrate and by the state of health of the intestinal cells.

A Comparison of the Metabolism of Some Mineral Constituents of Cows' Milk and of Breast Milk in the Same Infant.—WANG, WITT and FELCHER (*Am. Jour. Dis. Child.*, 1924, 27, 352) found that, owing to failure completely to evacuate the bowels every twenty-four hours, accurate determinations can be secured only from the average values of at least a three-day period. A change from breast milk to cows' milk, or *vice versa*, was invariably accompanied by a change in the quantity of calcium excreted in the feces. The actual quantity was always greater on a diet of cows' milk. The difference in the calcium excretions of the same child ranged from 0.0726 to 0.7829 gm., with an average of 0.4364 gm. The difference in the calcium excretion in the urine brought on by a change in the diet is slight and inconsistent. Calcium absorption and retention run closely parallel, since the variation in the urinary calcium output is slight and of little significance. The actual quantity of calcium absorbed and retained is greater for cows' milk than for breast milk, but percentage utilization and retention is greater from breast milk, except for older children. With cows' milk the average utilization is 0.7094 gm. per twenty-four hours, and with breast milk 0.4433 gm. The percentage utilization of cows' milk is 47.5 and of breast milk is 63. The figures for calcium retention show an average of 0.8025 gm. per twenty-four hours for cows' milk and 0.4524 gm. for breast milk, or a percentage retention in cows' milk of 46.1 and for breast milk 60.9. The calcium metabolism of breast milk is independent of the age of the child, but that of cows' milk shows a distinct increase with the age of the child both in individual cases and in the group of subjects. The percentage utilization and retention of calcium of breast milk in infants from 1.4 to 5.7 months falls within a range of 10 per cent. In case of cows' milk with children from 0.4 to 6.1 months there is a range of 27 per cent in utilization and 28.4 per cent in retention, the higher figures occurring in the older children.

Arsenic in Human Milk after Intravenous Injections of Arsphenamin.—FORDYCE, ROSEN and MYERS (*Am. Jour. Syph.*, 1924, 8, 65) examined seventy-five specimens of milk taken from twelve nursing mothers under treatment for syphilis. It was found that after intravenous medication with the arsenicals breast milk shows definite amounts of arsenic after various intervals corresponding in some individuals to the amounts found in the blood of treated individuals after the same lapse of time. The presence of arsenic in mother's milk is more constant than in either the blood or urine, and is found in appreciable amounts long after its administration. The deduction is made that a suckling probably receives sufficient arsenic in its daily feedings to be of some therapeutic value. For this reason the energetic treatment of syphilitic mothers during lactation is advisable.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Pregnancy after Bilateral Amputation of the Breasts.—SCHNEIDER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 64, 295) reports the case of a woman, aged thirty-seven years, in her second pregnancy, who had been in the tropics where she had contracted a parasitic disease, in the course of which hardened areas had appeared in both breasts, for which they had been removed. When aged thirty-six years a pregnancy occurred during which she complained of irregularity of action of the heart, acidity and at times vomiting. During the later portion of pregnancy there was a yellowish discharge. No evidence of syphilis or gonorrhea was present. The patient was brought into the hospital in labor. She was intensely nervous and over the anterior surface of the chest were large scars where the breasts had been removed. The knee-jerks were exaggerated but other reflexes were normal; the urine was normal. Labor proceeded spontaneously and a well-developed child was born. The puerperal period proceeded normally and the patient was discharged in good condition. The case is interesting in view of the fact that it is commonly supposed that there is a close relation between the development and functions of the mammary glands and the uterus; furthermore, it is known that mammary glands and ovaries act in reciprocal relation. It is interesting to observe that this case proceeded normally and that the only variation from a perfectly natural process, was the inevitable failure of breast milk in the nourishment of the child. The infant lost weight after birth to a considerable extent, but was finally well-nourished by artificial feeding.

Hemolytic Streptococci in Pregnancy.—KANTER and PILOT (*Surg., Gynec. and Obst.*, 1924, 38, 96) review the literature concerning the presence of streptococci in the vaginal secretions during pregnancy. The percentage in which these germs have been found by various observers varies from 4 to 40, and in these tabulations no effort is made to distinguish between hemolytic streptococci and others of the same group. During pregnancy the hemolytic streptococci vary from 2.5 to 50 per cent in cases examined by different investigators. Various explanations have been given for this discrepancy; some allege that it depends upon the manner in which the cultures were taken; others that the general condition of cleanliness in the body of the patient had much to do with the presence or absence of these germs. The idea that all hemolytic streptococci are virulent is not tenable at the present time. Some of the most recent observers believe that it is impossible to differentiate between streptococci existing in the lochial discharge in harmless form, and those causing infection. The writer studied 96 patients, among whom 19 had profuse vaginal discharge during pregnancy, 67 a moderate discharge and 10 had none. There were 19 abnormal and 67 of what might be termed average discharge. Three cultures were obtained—one from the lateral wall of the vagina after separating the labia, the second from the posterior fornix and the third from the os uteri. In obtaining the two latter a sterile speculum was used; the swabs so innoculated were brought in contact with an infusion of agar, to which defibrinated human blood was added—1 part of blood to 1 of agar. Readings were made at the end of twenty-four and forty-eight hours. The germs found were further identified by various forms of culture, and in some cases these were injected into rabbits. From these tests it is interesting to note that these bacteria appear less virulent than streptococci found in the tonsils and nasopharynx of patients. As to the source of these streptococci they evidently were present in the vagina before labor or were introduced by the hands or instruments of those who attended the patient, while some of them undoubtedly came from the throats of attending physicians and nurses, and in some cases the focus of infection was located in the throat, nose or sinus of the patient herself. These observers found the hemolytic streptococci rarely present in the normal vagina and believe that hemolytic streptococci infections arise from without the body of the patient. Droplets of secretion from the throat and nose of attendants and patients are usually conveyed into the bodies of patients by examination and operation, and these droplets often contain hemolytic streptococci. Sneezing or coughing by operators or attendants during an obstetric operation or delivery may also convey germs to the patient, for it has been shown that a normal throat contains hemolytic streptococci in practically 100 per cent of individuals. If a sore throat is present the streptococcus has added virulence and is more dangerous to the pregnant woman. It is also true that the patient's own throat may furnish pathogenic organisms leading to hemotogenic infection of the genital tract. A reasonable precaution in conducting labors would be for attendants and nurses to wear a gauze face mask, to exclude from delivery rooms persons having a sore throat and to isolate all patients who develop a streptococcic sore throat. These researches call atten-

tion to the familiar fact that manipulation of the birth canal or examination or operation increases the possibility of infection.

The Transmission of Arsenic from Mother to Fetus.—The question as to the passage of drugs and various substances from mother to child has always been of considerable practical interest. UNDERHILL and AMATRUDA (*Jour. Am. Med. Assn.*, 1923, 81, 2009) have reviewed the literature of the subject, finding that there are two antagonistic theories concerning placental transmission. One is that the chorionic epithelium takes a specific vital part in interchanges which occur in the placenta. The other theory considers the chorionic epithelium as a passive membrane whose action conforms to the laws of osmosis and diffusion. The discovery of enzymes in the placenta supports the vitalistic theory. Many of these enzymes have to do only with the living process of the cell in which they are found. Others state that placental transmission cannot be explained merely by mechanical laws because there is a greater concentration of the sodium and potassium salts in the fetal than in the maternal blood. Perhaps the majority of opinion is in favor of the mechanical theory of placental osmosis and diffusion. We know that nutritious material and oxygen pass from mother to fetus and waste products from fetus to mother. Various substances have been proven to pass through the placenta. These have been divided into those soluble in water and diffusible and those insoluble in water and not diffusible, which do not transverse the placenta. If the blood of the mother and fetus at the time of delivery is examined, the result strengthens the mechanical view; there is the same average of uric acid, creatin in the same concentration in maternal and fetal blood, the urea and non-protein nitrogen are the same, the percentage of sugar is slightly lower in fetal blood at the time of delivery. On the other hand, an excess of amino-acid appears in favor of the fetus. It has been shown that fetal and maternal blood are under the same osmotic pressure. Toxins, antitoxins and other products readily pass through the placenta in the same concentration. The mother's blood contains more non-diffusible fats and colloids than does the fetal. In the syncytium, iron, fat and albuminous substances undergo radical changes before entering the fetal circulation. The writers experimented upon animals by injecting neo-arsphenamin intravenously. These experiments show that arsenic is stored up in the placenta and maternal liver as contrasted with fetal tissue. Arsenic is transmitted through the placenta in small quantities, but evidently it is not stored in the fetal tissues which is a fact of considerable clinical importance. This would indicate that the drug can safely be given to pregnant women in the treatment of syphilis in the ordinary doses given to man and non-pregnant women without danger of injury to the fetus. It is a clinical observation that antenatal treatment of syphilis is efficient for the fetus. This seems to be due to the fact that arsenic can act in greater concentration on the spirochetes in the placenta where the drug is stored after serial injection, the drug has a more direct access to the spirochetes in the placenta, owing to the greater vascularity of this organ. The writers found that arsenic is detected in small traces in the fetal tissues after the intravenous injection of neo-arsphenamin into the maternal cir-

culation. The amount of arsenic recovered from the fetal tissues does not increase in proportion to the number of injections given. The drug is stored in the maternal liver and placenta increasing with the number of doses given.

The Prophylactic Treatment of Eclampsia by Artificial Light.—HOCKENBICKLER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, 62, 269) narrates his results in one of the clinics in the Vienna Hospital in the treatment of 50 primiparous patients, near term, who had increased blood-pressure, edema, albuminuria and headache, and 10 cases of eclampsia during labor and 2 postpartum. The entire surface of the body was irradiated, and the source of light is placed about 18 inches from the patient. The treatment is continued twenty minutes for the first day, five minutes upon each of four portions of the body. The duration is increased until pigmentation begins to appear. After this the treatment is given three days weekly and the lessened blood-pressure is taken as a favorable result. The quantity of urine is also measured and when this was a favorable symptom the treatment was increased to ten minutes. Of the 12 eclamptic patients 11 received but one treatment ten minutes in duration. The mammary glands and the vulva were covered with gauze during the treatment, and when the patient was blonde an erythema developed, which in 1 case was followed by the development of small vesicles over an area as large as a small plate; there was no other inconvenience or unfavorable result produced. The blood-pressure of the patient was taken, the patient was given a trial breakfast before the treatment and the quantity of urine carefully measured. It is thought that the treatment produced good by lessening the spasm of the capillary vessels, and that these spasms are largely responsible for the increased blood-pressure.

The Toxemia of Pregnancy.—WINDEYER (*Brit. Med. Jour.*, January 19, 1924) reported the results of 158 cases of eclampsia treated in the Royal Hospital for Women, Sidney, Australia. The mortality rate was 6.96 per cent. In 104 primiparæ there were 3 deaths; in 54 multiparæ, 8. The number of convulsions varied from 1 to 38. The infant mortality was 38 per cent. His experience indicates that when the patient had passed through a toxemic crisis, labor should be induced within a week to secure a living child. The treatment employed was eliminative and the compound jalap powder was freely used, morphin was employed in a considerable percentage of the cases, and veratrone when the convulsions persisted. Where there was persistent cyanosis and pressure of the right side of the heart, bleeding was practised. So far as obstetrical treatment was concerned, the tendency was to interfere as little as possible. The result of treatment has grown better, the writer believes, because the nursing of these patients was better done; there was less obstetrical interference, the convulsions were controlled by reducing blood-pressure until the bowels acted freely and the subcutaneous and intravenous injections of salines is avoided, because the kidneys did not act freely, as a rule, until twenty-four to forty-eight hours after delivery or after the cessation of convulsions.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY
OF PENNSYLVANIA, PHILADELPHIA.

Abdominoscopy.—Bearing in mind the invaluable aid which has been rendered to the gynecologist by the various types of endoscopes, especially the cystoscope, it is of considerable interest to direct our attention to the latest member of the endoscope family, the abdominoscope. This instrument devised by STEINER (*Surg., Gynec. and Obst.*, 1924, 38, 266) resembles the cystoscope and, as the curved end of the cystoscope was found to be very useful, it was made movable. The degree of curvature was regulated by a special mechanism at the opposite end of the instrument. To introduce the instrument with ease, he was careful to regulate the curvature at the end so that it was in the axis of the endoscope. The endoscope has a canal for the introduction of gas similar to the canal used in a cystoscope for irrigation purposes. The air-cock of the endoscope is connected to a bulb similar to that used on a blood-pressure apparatus. A 12-inch rubber tube which connects the air-cock to the bulb is divided by a glass tube which contains sterile cotton for cleaning the gas. A purgative is given the day before the examination and $\frac{1}{4}$ grain of morphin twenty minutes before puncture. The field of puncture is cleansed with benzine and then with alcohol and iodine. Local anesthesia with novocain is used, and it is a good plan to anesthetize also the adjacent peritoneum to prevent sensations during examination. A stab incision is made through the skin and a puncture done with the trocar inserted. Puncture should always be made with the abdominal muscles contracted. Usually there is a reflex contraction, but if none is present the patient is allowed to sit upright. The puncture must be carried out steadily and cautiously and to prevent deep entrance into the abdominal cavity, the trocar should be carefully steadied with the left hand while the abdominal wall is being penetrated. The trocar is removed and the abdominoscope is introduced along the tube which remains in the puncture canal. Then the tube is removed from the puncture canal in order that there may be an air-tight closure. The abdominal cavity is slowly inflated by means of the bulb, the abdominal wall offering very little resistance to the inflation. When the examination is finished the air is allowed to slowly escape, the endoscope is removed and with the hand placed flat on the belly, any remaining air is pressed out. The wound is closed with one suture, swabbed with iodine, and a small dressing applied. Of first importance in performing abdominoscopy is the original position and the correct changes of the position of the patient. As the air is of light specific gravity, it stays uppermost

in the abdominal cavity. Therefore, through changes in position of the patient, we are able to put the air in any place and thus displace the intestines at will. With the patient in a horizontal position, by moderate inflation there is presented a full view of all the organs in their normal relations under the abdominal wall. For an examination of the upper part of the abdomen the thorax is elevated and conversely, for an examination of the pelvis, the pelvis is elevated above the horizontal. For this purpose a safe and easily changeable table is essential. Steiner states that puncture in the lower part of the abdomen with the pelvis greatly elevated shows a beautiful endoscopical picture; in fact, the uterus, tubes, ovaries and sigmoid could have been shown very little better by laparotomy. If carefully performed the puncture is without danger, and there have been no complications observed following the use of this diagnostic procedure. The patients are allowed to get up the next day after the examination.

Relation of the Endometrium to Ovarian Function.—It is the belief of NORRIS and VOGT (*Surg., Gynec. and Obst.*, 1924, 38, 33) that the endometrium possesses a definite endocrinal function and that this function operates in conjunction with the secretory function of the ovary and is probably subservient to the latter. This theory is at present based only upon physiological and clinical proof. The fact that the endometrium differs histologically from other endocrinal glands is no argument against the theory, since all other endocrinal glands differ one from the other in this respect. They believe that this endocrinal function of the endometrium probably fluctuates with the menstrual cycle, being most active during the premenstrual period. The chief clinical evidence on which this theory is based lies in the established fact that the proportion of women who suffer from nervous phenomena after a hysterectomy with conservation of one or both ovaries is much greater than that of those who exhibit painful or palpable changes in the conserved ovary. The most conclusive evidence is found in those patients who have been treated with radium for the arrest of benign hemorrhages. It is difficult to conceive that in almost every case so treated both ovaries are rendered functionless. Furthermore, there is much experimental evidence that tends to show that in these cases the action of radium is limited to the uterus. The writers are of the opinion that in operations upon the uterus, ovarian conservation is of distinct value, even if panhysterectomy is performed; the ovaries function better, however, and have a longer functional life if a portion of the endometrium can be preserved. The thickened and permanent premenstrual stage of the endometrium, so frequently present in patients suffering from uterine myomata, is the result of stimulation of the endometrium by the presence of the tumor, and accounts for the prolonged bleeding that is often present.

Results of Operation for Retroversion.—In a follow-up study conducted by BLOOMFIELD (*Lancet*, 1924, 206, 227) to determine the results which are obtained by abdominal operations for uterine retroversion, answers were obtained from 50 patients, of whom 27 attended at hospital for examination and 23 sent written replies only. Ten (20 per cent) expressed themselves as cured, 26 (52 per cent) as relieved, while 14 (28 per cent) remained in *statu quo*. Information as to relief

of individual symptoms has been difficult to obtain, but it is of interest to note that of 25 patients complaining of menorrhagia, relief was obtained in 11; 21 complained of dysmenorrhea, of whom 16 were relieved; of the 41 who had constant pain before the operation 27 were relieved; of 18 patients who complained only of sterility 4 conceived following operation, while 1 of the 3 patients who complained of dyspareunia was relieved. Of the 10 cases who were cured complications were present in 8 cases at operation (80 per cent). In 26 cases who were only relieved complications were present in 21, or approximately 60 per cent; while in the 14 cases who remained the same, only 71 per cent had complications. In the 27 cases who reported for examination the uterus was found anteverted in 22 cases, of whom 12 (55 per cent) were relieved, and retroverted in 5 cases, of whom 3 (60 per cent) were relieved. As a result of this study Bloomfield states that retroversion is not a disease in itself and practically never gives rise to a definite train of symptoms. It is usually complicated by other pathological findings and it is these, as a rule, which indicate operative treatment, and upon which relief of symptoms largely depends. In this series 80 per cent of cured cases were complicated, while only 70 per cent of cases that were unrelieved had complications. Possibly a longer series might show a more marked difference between the two. In cases where no complication is found on clinical examination, and sterility is complained of, operation is sometimes indicated, as closed tubes may be present and a better chance of conception seems to be given after dilatation of the cervix if the uterus is replaced and retained in the anteverted position. In many cases an undoubted nervous element is present, the significance of which must be carefully assessed before operative treatment is undertaken, and in considering the result of such treatment. Too few cases of pregnancy have occurred in this series to enable one to make any statement as to its effect, but from a consideration of the results given by other authors pregnancy does not seem to exert any deleterious effect on orthopedic and clinical results of treatment beyond the fact that it makes prolapsus more common and may, if symptoms recur, transfer the case to the type of retroversion which complicates prolapse, which Bloomfield believes, should not be considered as retroversion, but as prolapse and treated as such.

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,

PHILADELPHIA.

The Clinical Value of Tonometric Measurements.—BAILLIART (*Ann. d'ocul.*, 1924, 161, 81) concludes that tonometry is an acquisition

of great value which it is impossible to dispense with. It is a clinical method, and, like all such methods, it has its advantages and limitations. By its means it is possible to recognize hypertension in cases where the most expert finger is incapable of doing so, of measuring its progress and even, to a certain extent, its gravity. At the same time tonometric figures, except in extreme cases, have no absolute value in themselves; their value is, however, considerable when the measurements are regularly made with the same instrument upon the same patient. It is impossible at present to speak of tension constants in the sense of optical constants, and tonometry does not yet possess the objective value of ophthalmometry. Less attention should be paid to the figures themselves than to the relation with such as may be regarded as normal, or with such as have been found in previous examinations of the same patient. A thermometric curve may be graphed with two different thermometers; that a tonometric curve may be reliable, its elements must be supplied by the same tonometer.

One Hundred Cataract Operations Performed in One Day at Shikarpur, Sind, India.—HOLLAND (*Arch. Ophth.*, 1924, 53, 155) recounts the circumstances of the clinic and the operations performed by Fisher, of Chicago, upon 113 eyes, January 22, 1923, 13 of which were iridectomies for glaucoma or optical purposes and 100 for cataract, between 10 A.M. and 5.30 P.M., with one hour for lunch, giving six and one-half hours operating, or three hundred and ninety minutes, so that he did one operation every three and a half minutes. The clinic can be best described as an eye camp, lasting for six weeks each year (January 1 to February 15), during which some 8000 cases were dealt with. The wards are just like a large rambling eastern caravanserai, which accommodates about 1000 people. At the busiest time there are between 600 and 800 in-patients and only two English sisters and three ward orderlies as dressers, so that efficient supervision is out of the question, and yet, in spite of the many disadvantages, the end-results are very satisfactory; that year 1322 cataracts were operated upon. One great difficulty is the impossibility of arriving at a true history; the patients and their relatives will often wilfully mislead from fear that if they give a true history operation would be refused; many hopelessly blind patients often declare they have light perception, and often make fairly accurate guesses at counting fingers. Others again have an idea that if they admit light perception they will be rejected because the cataract is not ripe. For this reason several cases each year, surgically perfect, have no vision, and ophthalmoscopic examination reveals various fundus changes, such as retinitis pigmentosa, optic atrophy and so on. Another foe is trachoma, which with all its sequelæ and complications is the rule, and it is exceptional to find an eye free from all traces of this disease. Glaucoma is also extremely prevalent and a large number of the cataract cases have plus tension. This year out of a total of 7800 new out-patients there were 702 cases of glaucoma. The routine method of operating senile cataract is Smith's intracapsular, and the treatment is to dress the eyes of those not complaining, first on the fifth day and on the seventh, if there are no complications, to put on a shade, and the greater number leave on the seventh, eighth and ninth day after operation. Of the 100 cataract operations by Fisher the following immediate com-

plications occurred: Spoon deliveries, 6; burst capsules, 9; vitreous loss, 12; lens in vitreous, 1 (eye bandaged, lens easily removed from anterior chamber third day); expulsion of lens following the incision, 4. After-complications: Prolapse of iris, 3; slight incarceration of the iris in 5. Choroidal hemorrhage occurred in 2 cases; sepsis, 2 cases; hazy cornea, 2 cases; hyalitis, 2 cases; gaping wound, 1 case. Results: Good surgical results in 92 cases; otherwise in 8, of which 2 were due to choroidal hemorrhage, 2 to sepsis, 1 glaucomatous eye which should not have been operated upon and 3 in which there was no vision, probably due to retinal and choroidal changes. If 4 or 5 of the plus tension eyes operated upon had been excluded Dr. Fisher would have had 96 to 98 per cent of surgical successes. Postoperative inflammation is rare and needlings are not required except in a few of the cases of burst capsule.

Papillary Stasis and Decompressive Craniectomy.—VELPER (*Rev. d'oto-ocul.*, 1923, 1, 25) urges that in papillary stasis of intracranial origin, lumbar puncture should always precede any other operative procedure; it should be performed with precaution and repeated with prudence; it should likewise be accompanied by a course of mercury. If, after the expiration of eight or ten days at most, the results are uncertain, trephining should be resorted to without delay; the operation should be done under local anesthesia with the patient seated; the operation should be completed rapidly without exploratory maneuvering. Where precise localization of the lesion is impossible the section should be made in the subtemporal or temporo-parietal region; the dura mater is not to be incised except in cases where the tumor presents at once. The opening in the bone should be from 6 to 8 cm. in diameter. The visual disturbances begin to improve on the second or third day; the visual acuity increases and may become normal in from fifteen to twenty days. As a general rule, the improvement in the visual acuity is maintained; the ophthalmoscopic appearances change more slowly; in some cases several weeks or months are required for the papilla to resume its normal aspect. Slight improvement is always possible, even after complete loss of vision. Following trephining lumbar puncture may be repeated without risk. Definite cure can be obtained when the case is one of serous meningitis or ependymitis, but if tumor be present its evolution is almost never arrested.

Spontaneous Cure of Acute Retrobulbar Neuritis.—CHAILLOUS (*Laclin. ophth.*, 1924, 28, 112) recalls the opinion of some writers that acute retrobulbar neuritis is frequently due to unrecognized sphenoidal sinusitis; they thence conclude that these sinuses should be freely opened in cases of optic neuritis of unknown origin. The writer observes that it has been demonstrated that many cases of retrobulbar neuritis spontaneously tend to complete or almost complete recovery. He recalls four observations which confirm, in this matter, the conclusions of Lenoir and Weill. Hence opening the sphenoidal sinus should not be the rule in retrobulbar neuritis; such intervention should be reserved for cases in which rhinoscopical and radiographical examinations show a lesion of the sinus, or at least to cases of unknown origin in which there is no amelioration at the expiration of some weeks.

The Visual Fields in Empyema of the Nasal Accessory Sinuses in Nasal Anomalies and in Ozena.—BECK and PILLAT (*Klin. Monatsbl. f. Augenh.*, 1923, 7, 78) report examination of the ocular conditions in patients with the above anomalies—a matter bearing directly upon the question of operation in cases of retrobulbar neuritis of uncertain etiology. Of 91 patients with empyema, referred to different ophthalmologists for examination, 6 only showed departure from the normal, all of which, however, were within physiological limits, presenting no signs of retrobulbar neuritis. The authors next extended their researches to nasal anomalies, it having been supposed that certain varieties were a disposition to retrobulbar neuritis. The material examined included 47 patients with normal nasal conditions, 53 with empyema of a single accessory sinus, 64 with nasal anomalies and 25 with ozena. Of the first group 4 showed contractions or indications of scotoma; these would have been regarded as pathological in the presence of disease of the accessory sinuses. Of the second group, the empyemata, 6 showed departures from the normal, *i. e.*, contractions of the field in 3, enlargement of the blind spot in 3; central scotoma was found in none of the cases. The third group, anatomical anomalies of the nose, presented 5 abnormal findings, of which 1, a tabetic with retrobulbar neuritis, is to be excluded; the remainder showed enlargement of the blind spot, central scotomata and slight contraction of the field. Of the cases with ozena 2 only presented departures from the normal, 1 (positive Wassermann) left-sided contraction for red, the second slight enlargement of the blind spot for blue alone. The authors conclude from their researches that neither in empyemata nor in ozena, nor in gross anomalies of the nose are ocular changes found which can be referred with certainty to a retrobulbar neuritis. The question, therefore, arises whether in apparently normal conditions of the sinuses, when retrobulbar neuritis is present which has proved refractory to other therapeutic measures, it is justifiable to practice opening of the sinuses, especially where conditions in the nose are normal. This question must be answered positively, in as much as the danger of such interference is slight.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY, UNIVERSITY OF TORONTO, TORONTO, CANADA,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH; PITTSBURGH, PA.

A Comparison of the Ziehl-Neelson and Schulte-Tigges Methods of Staining Bacilli.—Having been impressed with the fact that many patients who exhibited signs of pulmonary tuberculosis gave a nega-

tive test for tubercle bacilli, SCHOUB (*Jour. Bacteriol.*, 1923, 8, 121) applied several different methods of staining in the hope of finding a more efficient procedure than the Ziehl-Neelson technic. After numerous endeavors it was found that the Schulte-Tigges method gave a higher percentage of positives. This method consists in flooding the heat-fixed slide with carbolfuchsin (10 cc of saturated solution of basic fuchsin in 95 per cent of alcohol and 90 cc of 5 per cent carbolic acid); heating the slide to steaming for one minute; washing off the excess stain with tap water and decolorizing with 10 per cent aqueous solution of sodium sulphite; washing thoroughly with tap water and counterstaining with a saturated solution of picric acid; washing with tap water, drying and examining. The tubercle bacilli are red and the background is pinkish-yellow. Parallel observations were conducted on 800 sputums, 244 of which were positive with the new stain and 183 with Ziehl-Neelson. No sputum was ever found positive with the Ziehl-Neelson method and negative with the new method, while the reverse was true in 33 per cent of the tests. In addition, by actual count of the bacilli in the various preparations, the new method revealed five times as many organisms as the Ziehl-Neelson. The author does not believe that his results corroborate the opinion of some—that all tubercle bacilli are acid-fast. He further attributes the success of the new stain partly to the counterstain (picric acid), but more especially to the decolorizer (sodium sulphite), which also clarifies the slide, consequently exposing more organisms. He concludes that the Schulte-Tigges method is easier than the Ziehl-Neelson, that it gives about 33 per cent more positives, that it exposes more than five times more organisms and that it abolishes the use of alcohol as a decolorizer.

The Vaccine Treatment of Asthma.—RACKEMANN and GRAHAM (*Jour. Immunol.*, 1923, 8, 295) reported 131 cases which received autogenous and stock vaccines for such conditions as chronic pulmonary emphysema, chronic cough, and asthma without emphysema. The autogenous vaccine consisted of twenty-four-hour dextrose broth cultures of organisms which were fished from the second blood-agar plate which has been inoculated with bacteria recovered from the original blood-agar plate on which the sputum had been spread. These organisms were washed three times in salt solution containing 0.5 per cent carbolic acid and killed by heating at 56° C. for one hour. Each cubic centimeter contained about 2,000,000,000 organisms but there was no attempt at accurate standardization. The autogenous vaccines were injected intradermally employing equal doses of the various bacteria and the one producing the greatest degree of local redness and swelling was selected for treatment. The initial dose was about 0.25 cc and was administered at intervals of five to seven days depending on the local reaction and was continued until a dose of 2,000,000,000 organisms was reached or until clinical improvement had been established. Treatment was abandoned if six good-sized doses failed to produce improvement or local reactions. Successful results occurred in those cases in which inoculations gave considerable local reaction. Four cases, however, showed improvement without local signs. The importance of local reaction plus the fact that the results with stock

vaccines were as good or better than those with autogenous vaccines led the authors to believe that the action of oil vaccines in asthma was non-specific. Of the entire series of 131 patients, 9 or 7 per cent were cured; 31, or 22 per cent were definitely benefited; 13, or 10 per cent were helped somewhat; 24, or 18.5 per cent were relieved temporarily and 54 or 41 per cent did not respond in any way.

Effect of Spices on Growth of *Clostridium Botulinum*.—Following a previous study on the effect of spices on the growth of various aërobic bacteria, BACHMANN (*Jour. Infect. Dis.*, 1923, 33, 236) investigated the action of such spices as cloves, cinnamon, allspice, ginger, nutmeg, cayenne pepper, white mustard and black mustard on 6 strains of *Clostridium botulinum*, derived from different sources, which were known to be capable of growing in mince meat. No inhibition of growth was found in 1 and 2 per cent of spice, but there was some retardation with allspice and cloves when 2.5 per cent was used. The bacteria formed toxin in the presence of this amount of spice. The author concluded that "spices as used in flavoring foods do not help to make the food safe if there is contamination with *Clostridium botulinum*" and admonishes that "for safety such foods as mince meat should be unquestionably sterilized or else heated to the boiling point before they are tasted."

Chemotherapy of Experimental Typhoid Carrier Condition.—Although numerous attempts both clinical and experimental have been made to sterilize the focus of infection in the typhoid carrier, the results have not been satisfactory. Having previously shown (*Jour. Infect. Dis.*, 1921, 29, 495) that a dyestuff of the triphenylmethane series, new fast green 3 B, had a certain value for clearing up rabbits experimentally infected with *Bacillus typhosus*, but also that embolic deaths occasionally occurred, BECKWITH (*Jour. Infect. Dis.*, 1923, 33, 457) continued his attempts to sterilize gall-bladders of experimental rabbits by various other chemicals. Accordingly, arsphenamin, neoarsphenamin, iodine and many acid dyestuffs were injected intravenously following the inoculation of typhoid bacilli into the gall-bladder. The dyestuffs were utilized in 0.5 per cent distilled water solutions. It was found that none of these were effective in eradicating the experimentally produced carrier state, although certain temporary changes in the growth habit of *Bacillus typhosus* were encountered as a result of intravenous injection of particular dyestuffs.

The Effect of Peptone on the Peripheral Circulation.—In studying what factors other than the influence of the large mass of smooth muscle in the hepatic veins of the dog has on the fall in arterial pressure in anaphylactic and peptone shock, SIMONDS and RANSON (*Jour. Exper. Med.*, 1923, 38, 275) injected peptone solution into the iliac circulation of 7 dogs and horse serum into 1 sensitized dog. The peptone was inoculated into the left iliac artery by introducing it into the severed right iliac artery, so that the conditions of experimentation permitted of a normal blood supply in a normal manner. The effect was noted by recording the changes in leg volume by means of a plethysmograph and the carotid blood-pressure was taken with a mercury manometer, both instruments writing on the same kymograph. It

was found that injection of the peptone solution directly into the artery of the leg of a dog was followed by an abrupt increase in leg volume, which was of short duration and was followed quickly, usually in less than one-half minute, by a decrease in the volume of the limb below that previous to the injection. The phases of the leg volume curve bore a fairly definite relation to the changes in arterial pressure. The authors believe that their results indicate "That the long-continued low arterial pressure in peptone shock, and probably in anaphylactic shock, may be hastened but is not maintained by peripheral dilatation, and suggest that there is an impounding of the blood in some other part of the body."

Iodin Metabolism on Normal Diet in Relation to Prevention of Goiter.—McCLENDON and HATHAWAY (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 129) call attention to the fact that "It would require two thousand years to drink enough Lake Superior water to accumulate 20 mg. of iodine, and since the normal adult thyroid contains about this quantity and at least 50 per cent of persons drinking this or similar water escape goiter, there must be iodine in foods." They found that a man living in a moderately goitrous region (Minneapolis), consumed 0.057 mg. of iodine in three days on a normal diet, and excreted 0.021 mg. of iodine during the same period, having retained 0.036 mg. of iodine in three days. At this rate it would require about five years to accumulate 20 mg. of iodine. From tables they give, the authors show that persons eating much roughage (wheat, peeled and cored apples, oats, spinach and string beans) and drinking considerable quantities of milk of herbivorous animals would be immune to goiter.

The Acid-base Balance in Pneumonia.—While studying the respiratory and metabolic disturbances occurring in pneumonia, HASTINGS, NEILL, MORGAN and BINGER (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 66) determined the acid-base balance and the arterial oxygen unsaturation of pneumonia patients. Thirty observations made on 16 patients, indicated that almost all of the points, as plotted on the Van Slyke acid-base diagram, so modified as to include iso-CO₂ tension lines, were well within the normal acid-base area. In no instance was an uncompensated acidosis encountered, nor were there any cases of sufficient severity to indicate bicarbonate therapy. In 8 instances, in which repeated observations of the acid-base condition of the same patients were made, it was found that during the febrile period the CO₂ tension tended to be lower and the pH higher than after the temperature had returned to normal. The authors state that these results "Indicate that during the febrile period there is overstimulation of the respiratory mechanism which leads to a lower CO₂ tension and a slightly higher pH, but that this disturbance does not usually remove the patient from a normal acid-base condition." No direct relation between the degree of oxygen unsaturation and the low CO₂ tension of the febrile period was found.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL,
BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE,
WASHINGTON, D. C.

Chronic Carbon Monoxide Poisoning.—EGDAHL (*Jour. Am. Med. Assn.*, 1923, 81, 281) states that chronic carbon monoxide poisoning, although recognized for a long time, has not been given the attention it deserves by the medical profession. As the chances for exposure to carbon monoxide are so great, it would be well for the physician to keep in mind the possibility of chronic poisoning when a patient presents himself with ill-defined symptoms which cannot be explained otherwise. Repeated exposures to carbon monoxide, but not in sufficient degree to cause acute poisoning, will cause symptoms similar to the results of fatigue, and can be explained by lowered amount of oxygen in the blood. Just as a state of continued fatigue, so will a state of chronic carbon monoxide poisoning lower the resistance to various infections, or favor renewed activity of an old process. When there is a possibility of exposure to carbon monoxide, it would be well to make a blood test. By the use of various simple laboratory tests, it is possible to diagnose an early, or a presymptomatic stage of chronic poisoning and ward off the possibility of serious results. Preventive medicine has here a new field. Carbon monoxide poisoning is no longer confined to certain industries; the chances for poisoning are universal.

Effect of Acidification on Toxicity of B. Botulinus Toxin.—GEIGER and GOUWENS (*Pub. Health Reports*, 1923, 38, 2249) discuss previous work showing that acidification increases the toxicity; they describe their own experiments and present the following summary and conclusions: (1) Toxins of four strains of *Bacillus botulinus* were not increased in potency at any hydrogen-ion concentration, regardless of the length of time of exposure. The acid mixtures employed in this study were hydrochloric acid-sodium citrate and acetic acid-sodium acetate mixtures; (2) the injection of 1 cc of a buffered acetic acid of pH 4.0 causes the death of mice; this occurs whether *Bacillus botulinus* toxin is present or absent; with greater concentration of the hydrogen ions, death is more rapid, and less than 1 cc is sufficient to cause death in twenty four hours; (3) hydrochloric acid-sodium citrate, hydrochloric acid-potassium acid phthalate, and lactic acid-calcium lactate mixtures between the limits pH 4.0 and 2.3 do not kill white mice when injected intraperitoneally in 1 cc amounts. The acetic acid therefore appears to have a selective action upon white mice. This is not due to the acetate ions or undissociated sodium acetate molecules alone.

Child Mortality with Reference to the Higher Education of Parents.

—LENNOX (*Am. Jour. Hyg.*, 1924, 4, 52) has tabulated statistics from a group of 939 families, reporting 2475 pregnancies, with reference to the medical and general education of parents. He states that families in which the father is a doctor do not have lower mortality rates among children than the other professional or business groups. The small group of doctors engaged in a specialty show unusually high rates. Miscarriage rates for doctors' wives are high, probably because reports from other occupational groups are falsely low. College attendance of a parent or extended years of schooling is accompanied by slightly higher mortality rates of children. In case both parents have attended college or had extended schooling, there is a slightly lowered mortality rate. A disproportionate number of children whose parents have had less than a grammar school education have died of infectious diseases. The more highly educated parents report a larger proportion of living children who are in robust health. The above conclusions apply to a comparatively small group of persons. The question raised is of sufficient importance to warrant securing further evidence from much larger groups in various sections of the country.

Studies in Cancer.—BURROWS (*Proc. Soc. Exper. Biol. and Med.*, 1923, 21, 82) reports the results of his investigations on: The effect of circulation on the functional activity, migration and growth of tissue cells; the significance of the effect of circulation on the growth of cells; cellular growth and degeneration in the organism; factors regulating the production of cancer in the organism. He states, in conclusion, that cancer may be the normal outcome of any substance or condition capable of building a densely cellular tissue in the organism associated with an orderly decrease in the blood supply. It is not the result of any primary changes in the cell but to a specific rearrangement of cells, intracellular substances and bloodvessels in the organism.

Studies on Typhus Virus in the Louse.—BREINL (*Jour. Infect. Dis.*, 1924, 34, 1) found it possible to pass the typhus virus from louse to louse repeatedly with Weigl's method of injection. The course of the disease after injection of emulsified louse intestines differs from that after injection with virulent guinea-pig brain in those points: (a) In the guinea-pig the period of latency is generally much shorter; often the fever is abridged or interrupted by periods of normal temperature, and the height of the fever curve is less than after infection with guinea-pig virus; some animals die of the infection. (b) The agglutinin for the strain used appears much sooner in the rabbit after injection of louse virus; as a rule, the half of the maximal titer is reached on the seventh day. Production of agglutinin and active immunity can also be obtained in the rabbit by injecting emulsified louse intestines, to which phenol has been added. Guinea-pigs can be immunized also by repeated treatment with dead louse virus. The peculiarities of the infection following the injection of the louse virus are explained by the coëxistence of dead and living virus. The typhus virus multiplies considerably within the louse, but does not become more virulent. Ten days after infection the intestines of a louse contain 100 doses of living virus. The body of the louse contains only small quantities

of virus after the intestines have been removed. From this fact we can draw conclusions as to the way of natural infection in man. Lice fed on a patient one day after the fever had disappeared proved to be infectious seven days later. It is possible to infect lice with an emulsion of virulent guinea-pig brain.

The Cultivation of the Microorganisms of Rocky Mountain Spotted Fever (*Dermacentroxenus Rickettsi*) and of Typhus (*Rickettsia Pro-wazeki*) in Tissue Plasma Cultures.—WOLBACH and SCHLESINGER (*Jour. Med. Res.*, 1923, 44, 231) state that the virus of Rocky Mountain spotted fever and the virus of typhus survive in tissue-plasma cultures for a length of time corresponding to the survival of the endothelial cells multiplying in the cultures. The survival of the virus may be extended by "subcultures," a procedure which involves the washing of the tissue in Ringer's solution, and the addition of fresh plasma in order to permit the continuation of growth of the tissue cells. In both instances the microorganisms associated with the two diseases appeared in endothelial cells in the tissue cultures, in such numbers as to admit of no other explanation than that of multiplication. In the case of Rocky Mountain spotted fever a filamentous form appeared in the cultures in addition to forms previously described in arachnoid and mammalian tissues. In the case of typhus, coccoid, bacillary and filamentous forms appeared in exact duplication of the morphology of *Rickettsia prowazeki*, as described in lice infected with typhus.

Methods of Administering Iodin for Prophylaxis of Endemic Goiter.—OLESON (*U. S. Pub. Health Repts.*, 1924, 39, 45) reviews briefly the iodine prophylaxis in goiter. Reference is made to administration by inhalation and external application, but it is pointed out that internal administration is the most satisfactory means. Various forms of oral administration are referred to and the favorable results from chocolate tablets containing sodium iodide are especially noted. Iodized table salt is also referred to as well as iodized drinking water, but both are regarded as in the experimental stage. The possible disadvantages of rather indiscriminate iodine medication are mentioned. The author believes that in goitrous areas both boys and girls should receive the prophylactic and that the administration should be begin as early as eight years of age.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this JOURNAL.*

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *providing the request for them be written on the manuscript.*

All communications should be addressed to—

DR. JOHN H. MUSSER, JR., 262 S. 21st Street, Philadelphia, Pa., U. S. A.

INDEX.

A

- ABDOMINOSCOPY, 918
Abramson, H. A., relationship between the current of injury and the white-blood cell in inflammation, 702
Abscesses descending into neck and mediastinum, 614
Accident during delivery at term, 458
Acidity of gastric contents of infants, 454
 of infants' stools, 912
Alcohol a factor in eliminating racial degeneracy, 469
Allen, F. M., dietetic management of diabetes, 554
Anemia, pernicious, history of patients with, 758
 sickle-cell, 292
Anthrax treated by anti-anthrax serum, 255
Appendicitis, chronic, and its differential diagnosis, 864
Arsenic in human milk, 914
 in nervous system in treated neurosyphilis, 614
 transmission of, from mother to fetus, 916
Arsphenamine, reactions of, 142
 in syphilis, 292
Arthritis, rheumatoid, 275
Arthroplasty, 448
Aschner, P. W., diagnosis and management of supravescical hematurias, 225
Asthma, etiology of, 203
 vaccine treatment of, 924
Atophanyl, experiences with, 452

B

- B. BOTULINUS toxin, toxicity of, 927
Bacillus acidophilus milk, 141
 botulinus, spores of, 154
Bacteriology, of fatal infection following abortion, 146
Bar, interureteral, 607
Barry, M. W., medical biliary drainage, 368
Bell, J. R., variations in gastric secretion of the normal individual, 520
Bilharziasis of the ureter, 449
Biliary drainage, 368

- Bismuth in treatment of syphilis, 293
Bladder tumors, 771
Block, spinal subarachnoid, 293
Blood counts and basal metabolism of leukemia under roentgen-ray treatment, 29
 sugar during pregnancy, 145
Blood-pressure in the newborn, 611
 studies in normal pregnancy, 146
Boardman, W. W., bacteriological findings in the Lyon-Meltzer test, 847
Body, invasion of, by bacteria, 151
Botulinus antitoxin, efficacy of, 780
Bone cysts, benign, 609
Bowel, relation of, to B. coli kidney infections, 450
Brain abscess, 763
Breasts, pregnancy after amputation of, 914
Bronchi, experimental closure of, 762
Bronchial breathing, 447
 moniliosis, 446
Bronchopneumonia following measles, 606
Bryant, J., growth and length of the human intestine, 499
Butter-flour mixture, 612

C

- CANCER of the cervix, 148
 studies in, 928
Carbon monoxide poisoning, 927
Carbuncles, treatment of, 295
Carcinoma of the bladder with metastasis to the brain, 434
 of the breast, 908
 of the colon, 761
 of the papilla of Vater, 764
Cardiorrhaphy in acute injuries, 449
Carter, B. N., malignant tumor of the pancreas, 76
Cataract operations, 921
Child mortality, 928
Children, cardiac infections in, 300
Chlorosis, 134
 disappearance of, 606
Cholecystic disease, 907
Chronic malaria, 138
Cisterna magna, puncture of, 138
Clostridium botulinum, 925
 manner in which the toxin acts upon the body, 156

Cockrell, J. R., cerebrospinal fluid in encephalitis lethargica, 696
 Colds, studies on secretions from, 154
 Colitis in childhood, 300
 Colon, diseases of, 909
 Conjunctiva, folliculitis of, 778
 Conner, H. Milton, diaphragmatic hernia of the short esophagus type, 672
 Cord crushes, 449
 Courtney, R. H., accuracy of the cat method for the assay of digitalis, 816
 Craver, L. F., physical signs in the early detection of pulmonary metastases, 852

D

DEATH time of spores of *Clostridium botulinum*, 155
 Dermatitis venenata, 303
 Devil's grip in Virginia, 312
 Diabetes, dietetic management of, 554
 Wassermann reaction in, 768
 Diabetic patient, management of, 189
 Digitalis, accuracy of cat method for assay of, 816
 Diphtheria carriers among school population, 455
 Diverticulum of the urinary bladder, 763
 Dock, W., ventricular rhythm, 664
 Du Bray, E. S., management of patients presenting essential hypertension, 710
 Duodenal ulcer, 136
 Dysentery, flagellate, 298

E

ECLAMPSIA, treatment of, by artificial light, 917
 Edmondson, C. C., use of insulin in diabetes, 570
 Elimination of carbon monoxide from blood, 779
 Empyema of the nasal sinuses, 923
 Encephalitis lethargica, cerebrospinal fluid in, 696
 Endothermy in neoplastic diseases, 763
 Enterocolitis, tuberculous, 450
 Enucleation, intracervical, 306
 Epstein, J., studies in electroionic medication, 625
 Esophagus, perforation of the, due to instrumentation, 194

F

FINEMAN, S., diaphragmatic hernia of the short esophagus type, 672
 Flipse, M. J., malignant tumor of the pancreas, 76

Foerster, H. R., sporotrichosis, 54
 Food tests, biological, 140
 Foot, N. C., malignant tumor of the pancreas, 76
 Foss, H. L., relationship of goiter to mental disorders, 724
 Foster, H. E., cerebrospinal fluid in encephalitis lethargica, 696
 Friedenwald, J., perforation of the esophagus due to instrumentation, 194
 Fusiform bacilli and spirochetes in otitis media chronica, 467
 in tonsils and adenoids, 466

G

GALL-BLADDER disease, management of, 296
 pathology, 295
 Gall stones in dogs, 151
 Gastric secretion, effects of alkalis on, 298
 variations in, of the normal individual, 520
 Gastro-intestinal findings in adult eczema, 615
 Gestation, late ectopic, 150
 Gilbert, O. O., clinicopathological study of acute meningo-encephalitis, 781
 Glaucoma and syphilis, 461
 Glycosuria in gall-bladder and duct diseases, 1
 Goiter, exophthalmic, 907
 roentgen-ray therapy in treatment of, 38
 Goodwin, G. M., roentgen-ray therapy in exophthalmic goiter, 38
 Granuloma inguinale, 143
 Gray oil, absorption of, 144
 Gurd, A. E., clinicopathological study of acute meningo-encephalitis, 781
 Gutmann, B., leukemia, 718

H

HACHEN, D. S., use of insulin in modern treatment of diabetes, 403
 Haden, R. L., relation of non-protein nitrogen of blood to parathyroid tetany, 108
 Hamilton, C. E., disease of the mediastinum and its contents, 888
 Harbinson, C. H., effects of roentgen-ray energy on the spleen, 529
 Haskell, C. C., accuracy of the cat method for the assay of digitalis, 816
 Hay fever with optochin hydrochloride, 137
 Health department, changes brought about by, 311

Hearts, changes in size and shape, during progress of compensation, 606
 Held, I. W., chronic appendicitis and its differential diagnosis, 864
 Hematurias, diagnosis and management of, 225
 Hemoglobin, excretion of, by the kidney, 152
 Hemorrhage, meningeal, in the newborn, 910
 methods of controlling, 297
 Hernia, operations for, 294
 of the short esophagus type, 672
 "Hexeton," for hypodermic use, 610
 High-voltage roentgen-ray therapy, 608
 Hodgkin's disease, pathological changes in, 157, 313
 Housing and health, 467
 Howard, M. C., medical biliary drainage, 368
 Howard, T., syphilis of the heart and blood-vessels, 266
 Human intestine, growth and length of, 499
 Hydatidiform mole and chorio-epithelioma, 305
 Hydronephrosis, chloride retention in, 776
 Hyperglycemia in certain dermatoses, 446
 Hypophyseobasal area in its relation to diabetes insipidus and polyuria, 679

I

IMMUNIZATION against cholera per os, 134
 Inguinal hernia, 136
 Injury to fetal cranium and spinal column during labor, 617
 Inlow W. De P., spleen and digestion, 10
 Insulin in modern treatment of diabetes, 403
 therapy, outline of a routine for, 586
 in treatment of diabetes, 570
 Intestinal rupture, 136
 Iodide and bromide exanthems, 144
 Iodin metabolism on normal diet in goiter, 926
 for prophylaxis of endemic goiter, 929
 Isoagglutination in newborn infants and their mothers, 445

J

JACKSON, J. A., relationship of goiter to mental disorders, 724
 Jaundice, chronic hemolytic, 220
 Jonas, L., outline of a routine for insulin therapy, 586

Jones, C. M., studies in pancreatic function, 649

K

KELLERT, E., action of sodium bicarbonate upon the kidneys, 114
 Kilduffe, R. A., Kolmer modification of the complement-fixation test for syphilis, 392
 Klein, T., rheumatoid arthritis, 275
 Knee-joint, internal derangements of, 609
 Knock-knee and bow-leg, 763
 Kolmer modification of the complement-fixation test for syphilis, 392
 Kugelmass, I. N., studies in electro-ionic medication, 625

L

"LAUGHING" sign after extraction of cataract, 462
 Lemon, W. S., tuberculosis as an etiological factor in Hodgkin's disease, 178
 Leopold, S. S., postoperative massive pulmonary collapse and drowned lung, 421
 Leprosy, complement-fixation reaction as applied to, 308
 Wassermann reaction in, 144
 Leucorrhea, chronic, 619
 Leukemia, 718
 myeloid, treatment of, with thorium X, 758
 Leukoderma, syphilitic, 615
 Levine, S. A., ventricular rhythm, 664
 Lichty, J. A., glycosuria in gall-bladder and duct diseases, 1
 Life cycle of *Bacillus fusiformis*, 465
 Light, effect of, on organism, 455
 Liniae albicantes in varying degree in pregnancy, 459
 Lipoma, perirenal, 448
 Long, W. B., roentgen-ray therapy in exophthalmic goiter, 38
 Louse, typhus virus in the, 928
 Lower, W. E., primary carcinoma of the bladder with metastasis to the brain, 434
 Lumbago treated by quinine and urea, 611
 Lupus, erythematous, 302
 Lyon-Meltzer test, bacteriological findings in, 847

M

McALPIN, K. R., blood counts and basal metabolism of leukemias under roentgen-ray treatment, 29

McClure, C. W., studies in pancreatic function, 649
 McFarland, A. R., effect on the kidney of treatment for syphilis, 477
 MacAdam, W., variations in gastric secretion of the normal individual, 520
 Malignant tumor of the pancreas, 76
 Management of patients presenting essential hypertension, 710
 Measles, blood plasma and serum in prophylaxis of, 911
 immunity of infants with, 301
 in rabbits and monkeys, 312
 Medication, studies in electronic, 625
 Melanosis and argyria of the skin, 458
 Meningo-encephalitis, clinicopathological study of, 781
 Mesothelium, peritoneal, and formation of adhesions, 152
 Metabolism of cow's milk and breast milk in the same infant, 913
 readings in pregnant cases, 147
 Metastases, pulmonary, value of physical signs in early detection of, 852
 Method for estimation of blood fibrinogen, 134
 Microorganisms of spotted fever and typhus, 929
 Microscopical compared with clinical diagnosis of uterine cancer, 773
 Middleton, W. S., palpation of the spleen, 118
 Milk, acidified, whole, as an infant food, 299
 tubercle bacilli in, 312
 Miller, T. G., necrosis and gangrene of the urinary bladder, 339
 Morgan, Hugh, J., trypanisomiasis treated with tryparsamide, 827
 Morrison, T. H., perforation of the esophagus due to instrumentation, 194
 Musser, Jr. J. H., outline of a routine for insulin therapy, 586
 Myelitis, gonorrheal, 760

N

Necrosis and gangrene of the urinary bladder, 339
 Neosalvarsan treatment of gangrene of the lung, 610
 Neuritis, retrobulbar, 922
 Neurosyphilis, 447
 Nicely, W. E., use of insulin in diabetes, 570
 Nitrous-oxide-oxygen-ethanesal as a routine, 609

O

Oil, iodized, injection of, 291
 Operation shock, 762

Orr, T. G., relation of non-protein nitrogen of the blood to parathyroid tetany, 108
 Osteoarthritis in infants, tuberculous, 139
 Osteomyelitis, resection of long bones in, 448
 Ostheimer, A. J., syphilis as the cause of muscular atrophy of spinal origin, 835
 Ovarian function, relation of endometrium to, 919

P

PACK, G. T., studies in electroionic medication, 625
 Paget's disease of the female nipple, 909
 Pancreatic function, studies of, 649
 Parathyroid therapy, 452
 Patients pregnant and tuberculous, treatment of, 303
 Pellagra prevention by diet among institutional inmates, 623
 Pemphigus, etiology of, 144
 treatment of, 457
 Peptone, effect of, on peripheral circulation, 925
 Pertussis in hospitals, 766
 reactions in, 140
 Phagocytes in pneumonia, 621
 Phosphorus and calcium of the blood in renal disease, 759
 Pneumococcus immunity, 310
 Pneumonia, acid-base balance in, 926
 size of heart in, 293
 Porter, W. B., paroxysmal ventricular tachycardia, 821
 Pottenger, F. M., etiology of asthma, 203
 Pregnancy, hemolytic streptococci, 915
 sugar in urine during, 145
 in syphilis, influence of, 445
 toxemia of, 917
 Prostate, enlargement of, 608
 Protein therapy, 451
 Pulmonary collapse and drowned lung, 421
 Pyelitis, 767
 in the newborn, 147
 treatment of, 452
 Pyelographic medium, 772

R

RABBITS and monkeys, experimental
 measles in, 153
 pneumonia in, 621
 spirochetosis in, 309
 Rashes, recurrent serum, 777
 Rats, plague-infected, 156
 Regan, C., anthrax treated by anti-anthrax serum, 255

- Relationship between the current of injury and the white-blood cell in inflammation, 702
 of goiter to mental disorders, 724
 Relief after tonsil and adenoid operations, 454
 Results of a three-year trachoma campaign, 468
 Retroperitoneal and perinephric infection, 762
 Retroversion, results of operation for, 919
- Reviews—
 Abt, Pediatrics, 751
 Barnes, The Tonsils (Faucial, Lingual and Pharyngeal), 132
 Barnes, Mental Disorders, 444
 Bergey, Manual of Determinative Bacteriology, 126
 Bickham, Operative Surgery, 600
 Bowen, Anatomy and Kinesiology, 284
 Braun, Local Anesthesia, 748
 Brooks, Diagnostic Methods, 289
 Burrows, Mistakes and Accidents of Surgery, 440
 Cabot, Modern Urology, 749
 Cabot, Physical Diagnosis, 128
 Clarke, Protists and Disease, 286
 Collins, Arboreal Life and Evolution of the Human Eye, 285
 Core, Functional and Nervous Diseases, 440
 Davis, Neurologic Diagnosis, 905
 Deaver, Reimann, Excursions into Surgical Subjects, 756
 von Domarus, Grundriss der inneren Medizin, 902
 Dorland, Medical Dictionary, 901
 Drew, Gymnastics, 284
 Dutton, Intravenous Therapy, 750
 Eisenberg, Bacteriology, 127
 Ely, Inflammation in Bones and Joints, 602
 Falta, Endocrine Diseases, 129
 Finsterer, Burke, Local Anesthesia, 440
 Foster, Examination of Patients, 131
 Fowler, Problems in Tuberculosis, 906
 Graves, Gynecology, 130
 Griffith, J. P. C., Care of the Baby, 444
 Hegner, Taliaferro, Human, Protozoology, 603
 Hess, Infant Feeding, 439
 Huddleson, Food for the Diabetic, 901
 International Clinics, Volume III, 33d Series, 132
 International Clinics, Volume IV, 33d Series, 1923, 904
 Joslin, Diabetes Mellitus, 283
 Kellogg, New Dietetics, 289
- Reviews—
 Kelly, Walter Reed and Yellow Fever, 756
 Kerr, Ferguson, Young, Hendry, Obstetrics and Gynecology, 604
 Knowles, Diseases of Skin, 125
 Kolmer, Infection, Immunity and Biologic Therapy, 290
 Laird, Psychology for Nurses, 903
 Lawson, War Blindness at St. Dunstan's, 127
 Lyon, Drainage of Gall Tract, 900
 McFarland, Fighting Foes too Small to See, 905
 McNair, Rhus Dermatitis, 286
 Mariotte, Discours de la Nature de L'Air, 288
 Military Hospitals in the United States, Volume V, 904
 Misch, Lehrbuch der Grenzgebiete der Medizin und Zahnheilkunde, 902
 Morrey, Bacteriology, 285
 Morris, Laboratory Diagnosis, 903
 Mottram, Manual of Histology, 599
 Muthu, Pulmonary Tuberculosis, 599
 Myers, Analysis of Blood, 750
 Naegeli, Blutkrankheiten und Blutdiagnostik, 441
 Newman, H. H., Physiology of Twinning, 285
 Noguchi, Diagnosis of Syphilis, 442
 Pearl, Introduction to Medical Biometry and Statistics, 441
 Peters, Chemistry, 287
 Pratt, Intranasal Surgery, 750
 Reed, Obstetrics, 287
 Rollier, Rosselet, Schmid, Amstad, Gauvain, Saleeby, Heliotherapy, 438
 Rose, Physical Diagnosis, 443
 Shaffer, Orthopedic Surgery, 601
 Smith, Heart Records, 130
 Starling, Action of Alcohol on Man, 288
 Stevens, Practice of Medicine, 438
 Stevens, Therapeutics, 131
 Stewart, Diathermy and its Application to Pneumonia, 903
 Stone, Blood Chemistry, 128
 Sutton, Diseases of the Skin, 602
 Thomas, Dietary of Health and Disease, 126
 Tilney, Riley, Huntingdon, Central Nervous System, 443
 Tredgold, Mental Deficiency, 439
 Veronoff, Grafts from Monkey to Man, 755
 Watson, Hernia, 603
 Whitman, Orthopedic Surgery, 125
 Williams, Minor Maladies, 444

Reviews—

- Wilson, How Our Bodies Are Made, 906
 Reynolds, L., studies in pancreatic function, 649
 Rickets in the breast-fed infants, 765
 egg yolk in, 624
 Rickettsia in Rocky Mountain spotted fever, 153
 Roentgenography of urinary tract, 608
 Roentgenotherapy of condyloma, 768
 Roentgen-ray energy on the spleen, effects of, 529

S

- SACHS, A., medical biliary drainage, 386
 Sajous, C. E., de M., hypophyseobasal area in its relation to diabetes insipidus and polyuria, 679
 Salpingitis, treatment of, 769
 Sanger, B. J., blood counts and basal metabolism of leukemias under roentgen-ray treatment, 29
 Sarcoma of long bones, 909
 Scarlet fever, 613
 Schick tests against diphtheria, 310
 Schlaepfer, K., uncomplicated dislocations of the shoulder, 244
 Sclerecto-iridectomy in chronic glaucoma, 461
 Scleroderma, etiology of, 616
 Seminal vesicles, surgery of, 450
 Sharpe, N., atypical spinal tumor, 542
 Sheppe, W. M., torula infection in man, 91
 Shionoya, T., ultraviolet absorption spectra of cerebrospinal fluid, 735
 Shock, anaphylactic, 622
 Shoulder, uncomplicated dislocations of the, 244
 Sodium bicarbonate, action of, upon the kidneys, 114
 Spleen and digestion, 10
 palpation of, 118
 Splenectomy in hemorrhagic purpura, 134
 Sporotrichosis, 76
 Sprue, nature and treatment of, 610
 Stasis, pulmonary, and decompressive craniectomy, 922
 Statistical study of tuberculosis mortality, 133
 Stenosis, pyloric, treatment of, 761
 Stockard, C. R., alcohol a factor in eliminating racial degeneracy, 469
 Stoner, W. C., management of the diabetic patient, 189
 Sulfoxylsalvarsan, 137
 Suprarenal cortex, influence of, on the gonads of rabbits, 774
 Suprarenalectomy in rabbits, 622
 Surgery, value of cervical, 807
 Symmers, D., pathological changes in Hodgkin's disease, 157, 313

Sympathectomy, 607

- Syphilis, arsenobismuth treatment of, 605
 arsphenamine in, 303
 in the Bechuana and native, 768
 bismuth salts in treatment of, 456
 as the cause of muscular atrophy of spinal origin, 835
 cerebral, optic nerve in, 462
 effect on the kidney of, treatment for, 477
 as a factor in etiology of mental deficiency, 454
 of the heart and bloodvessels, 266
 marital, 302
 treatment of, with bismuth, 293
 with a new mercurial, 910
 with sulpharsphenamine, 612

T

- TACHYCARDIA, paroxysmal ventricular, 821
 Tetanus antitoxin, transmission of, through the placenta, 624
 Tetany during hyperpnea, causation of, 137
 parathyroid, 108
 Thymus irradiation in psoriatics, 457
 Thyroid, lingual, carcinoma of, 607
 Thyroidectomy in toxic goiter, 908
 Tonometric measurements, 920
 Tonsillitis, acute, 759
 Topography of larynx, trachea, and lungs in fetus, newborn infant and child, 453
 Torrey, R., rheumatoid arthritis, 275
 Torula infection in man, 91
 Toxic action of tobacco and alcohol upon the eye, 460
 Treponema pallidum, staining of, in dry smears, 757
 Trypanosomiasis treated with trypanamide, 827
 Tuberculosis, canine, 760
 as an etiological factor in Hodgkin's disease, 178
 pulmonary, 908
 unilateral pulmonary, 761
 Tumor, atypical spinal, 542
 of the kidney, 135
 Turpentine, studies of, 297
 Typhoid carrier condition, 925

U

- ULCERS of the jejunum and ileum, 764
 Ultraviolet absorption spectra of cerebrospinal fluid, 735
 Underhill, F. P., studies in electroionic medication, 625
 Ureter and bladder, studies on, 764
 Ureters in renal tuberculosis, 463

Urethritis in women, 149
 Urinary antiseptics, 762
 Uterine suspension, 464
 Uterus, prolapse of, hysteropexy for, 307

V

VACCINATION of the intestine against dysentery, 760
 technic and certification, 468
 Vaginitis, diphtheritic, in children, 774
 diphtheric, in children, 779
 Vasomotor tone during pregnancy, 304
 Ventricular rhythm, 664
 Vesical diverticula, 135
 Vesiculitis, seminal, vasostomy for, 295
 Vincent's agina with tryphaffavin, 297
 Vitamins, immunological significance of, 605, 775
 lack of, on leukocytes and phagocytes, 776
 Vulvitis, leukoplakic, 618
 Vulvovaginitis in children, 311

W

WASSERMANN reaction in spinal fluid, 142
 Watkins, R. M., primary carcinoma of the bladder with metastasis to the brain, 434
 Weber, F. P., chronic hemolytic jaundice, 220
 Wetmore, A. S., studies in pancreatic function, 649
 Wilson, G., syphilis as the cause of muscular atrophy of spinal origin, 835
 Winkelman, N. W., syphilis as the cause of muscular atrophy of spinal origin, 835
 Wolferth, C. C., necrosis and gangrene of the urinary bladder, 339
 Woods, J. O., glycosuria and duct disease, 1

Z

ZIEHL-NEELSON and Schulte-Tigges methods of staining bacilli, 923

